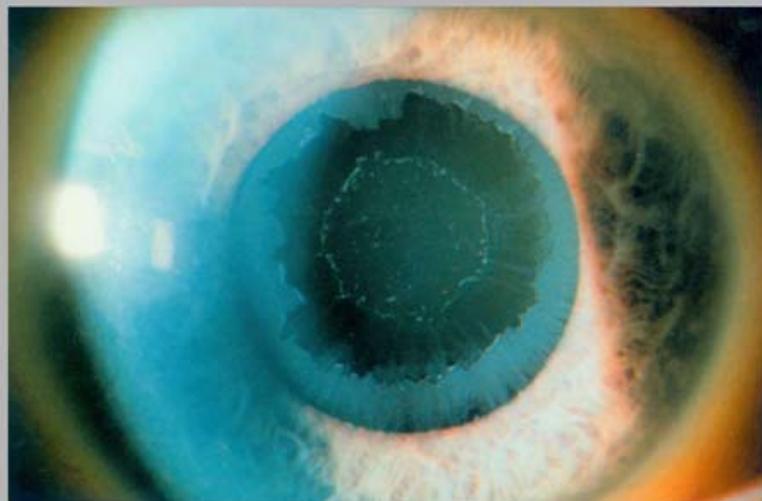


Glaucoma

Science and Practice



John C. Morrison
Irvin P. Pollack



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Edited by

John C. Morrison, M.D.
Professor of Ophthalmology
Oregon Health and Science University
And
Director of the Glaucoma Service
The Fred P. Thompson Glaucoma Clinic
and Casey Eye Institute
Portland, Oregon

Irvin P. Pollack, M.D.
Professor of Ophthalmology
The Johns Hopkins University
And
Emeritus
Ophthalmologist-In-Chief and
Director Krieger Eye Institute
Sinai Hospital of Baltimore
Baltimore Maryland

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Consulting Editor: Esther Gumpert
Editorial Assistant: Owen Zurhellen
Director, Production and Manufacturing: Anne Vinnicombe
Production Editor: Becky Dille
Marketing Director: Phyllis Gold
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To our wives, Lynne and Marlene
And to our families

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Foreword 1

Rapid advances in knowledge about glaucomatous diseases make it more difficult for textbooks to keep up-to-date. The increasing degree of sub-specialization and developments in technology, basic research, pharmacology, and surgery, further add to the problems encountered by efforts made to produce a timely, coherent, and inclusive glaucoma textbook by one or two authors. Multi-authored texts, on the one hand, often sacrifice uniformity of style and content and can introduce variations in quality as well as unnecessary duplication. On the other hand, they can provide the most timely expertise and stimulating controversial points of view. Most important, the juxtaposition of research and practice in such books requires the authors and the readers to attempt to bridge the gap between the laboratory and the clinical problems. Such two-way interactions are necessary if progress is to be made in "translational research." This can increase our understanding of the pathogenesis of the glaucomas, improve methods of diagnosis and treatment, and ultimately their prevention.

I have had the opportunity to review all chapters of *Glaucoma: Science and Practice* and found them to be up-to-date, stimulating and remarkably coherent. This is in no small part due to the excellent editorial work by Morrison and Pollock. They are to be congratulated for the organization of subjects and the selection of experts for each chapter, as well as the editing of the final product. This single volume should prove most useful to the student, resident or fellow who want to acquire authoritative information about all aspects of the disease. It also will appeal to the clinician and basic scientist, as well as stimulating the all-important potential clinician-scientist. It presents them with the current status of our knowledge, as well as confronting them with the outstanding problems presented by the glaucoma patient.

Bernard Becker, M.D.
St. Louis, Missouri

Foreword 2

Of the professorial aphorisms swirling amid those vulnerable first years of a new career, one indelibly seared my mind with a daunting, yet lasting, revelation: "You will be known by the people you train." Even now, as I sit in an audience, strange emotions stir whenever one of my former students ascends the podium. From their roots in the ancient world, physicians have always been called on both to heal and to teach, the latter, perhaps, the more sacred of duties. Healing helps one at a time, but the passing of the knowledge reaches millions for generations to come.

Teachers of medicine can feel no greater joy than when their own students embark on a project of sharing their knowledge, as one of my first glaucoma postgraduate fellows, Dr. John Morrison, with Dr. Irvin Pollack, has undertaken with this volume. To do so exhaustively, in a complete book of the science and practice of glaucoma, compounds the pleasure for the mentor. Drs Pollack and Morrison, editors of *Glaucoma: Science and Practice*, have assembled a remarkable group of expert authors, in many instances choosing among the most promising of their own students and colleagues, but always bringing the most valued experience and expertise to the page.

We live in a new Information Age, but some complain that random bytes so choke the wind as to defy interpretation. As never before, students, clinicians, and

the public struggle to separate scientific truth from smoky anecdotes generated from personal aggrandizement, academic survival, or aggressive marketing. Against the headwind of such data streams, students and clinicians yearn for information smelted in the crucible of credible scientific analysis. How appropriate, then, when a book on glaucoma opens with a discussion of epidemiology, that arcane key to interpretation of the data onslaught. The book devotes its first quarter to the science underlying the study of glaucoma. These clinician-scientist editors know that the understanding of the scientific basis for tests performed, diagnoses made and treatments available must underpin logical and successful glaucoma practice.

The book divides itself naturally into three segments, the scientific basis of glaucoma, the clinical entities of glaucoma and the therapy of glaucoma. The reader has available current information ranging from the very beginning of research on aqueous humor dynamics to the latest on the glaucoma genome. Here the novice can grasp the basis of glaucoma thought, how and where the aqueous flows, why and how the optic nerve becomes susceptible to damage, and how the intraocular pressure and optic nerve are measured. The chapters each stand alone as complete reviews of their individual subjects but

hang together in contiguity and continuity. For the purist, the text is all here, referenced both currently and historically. At the same time, for the more harried reader, side bars depict clinical Pearls, and Pitfalls. Highlighted Controversial Topics serve notice when not all the cognoscenti agree and spice the glaucoma fascination.

The second section addresses classification and various entities of clinical glaucoma as we now recognize them. Morrison and Pollack review the evolution of classification schemes over time from the anatomical differences apparent decades ago through the more subtle clinical differences recorded recently, and can only anticipate further modification in future decades. Even as we cherish our nineteenth century books, we willingly make allowances for nuances of classification in the context of contemporary knowledge. We expect further transition as genotypic differentiation becomes possible. In the meantime, the text provides an accurate and worthy guide through the morass of clinical entities of glaucoma.

As conceptual change in glaucoma inches forward with each addition to the scientific literature, modes of therapy, described in the third section, leap forward in incremental bounds with fanfare of new drug strategies or technical innovations. Thirty years ago, the options for

glaucoma therapy were few and generally unpleasant. Now, the choice of drugs is vast with many options within each new category, their nuances often more reflective of marketing and fashion than science. Laser surgery has found its way into a broad spectrum of modalities and incisional surgery offers a host of varieties. Considering the dramatic changes in therapy over the past two decades, perhaps these sections on treatment are most vulnerable to obsolesce within any book. To compensate, the editors have selected authors who bring the latest modalities, the basis from which they have sprung, and the directions toward which they point.

In the final analysis, physicians can derive comfort from books on the shelf, those from both the past and the present. For the practicing lifetime, they become ready and friendly consultants. When our time is finished, our books remain as icons of what we read, what we knew, what we valued and who we were. *Glaucoma: Science and Practice* will sit proudly among my books, as a manifestation of my investment in my student and an outstanding glaucoma reference in its own right.

E. Michael Van Buskirk, M.D.
Portland, Oregon

CONTRIBUTORS

Donald A. Abrams, M.D.

Assistant Professor of Ophthalmology
The Wilmer Ophthalmological Institute
The Johns Hopkins University
School of Medicine
And
Director, Glaucoma Service
Krieger Eye Institute
Sinai Hospital of Baltimore
Baltimore, Maryland

Ted S. Acott, Ph.D.

Professor of Ophthalmology and
Biochemistry and Molecular Biology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

P. Juhani Airaksinen, M.D., Ph.D.

Professor
Department of Ophthalmology
University of Oulu
Oulu
Finland

Monica Y. Allen-Alexander, M.D.

Assistant Professor
Department of Ophthalmology
Wayne State University
Kresge Eye Institute
Detroit, Michigan

Rommel Bautista, M.D.

Stanford University Medical Center
Stanford, California

Reay H. Brown, M.D.

Atlanta Ophthalmology Associates
Atlanta, Georgia

Carl B. Camras, M.D.

Chairman
Department of Ophthalmology
University of Nebraska Medical Center
Omaha, Nebraska

Joseph Caprioli, M.D.

Professor of Ophthalmology
Jules Stein Eye Institute
University of California at Los Angeles
Los Angeles, California

Anthony C. Castelbuono, M.D.

Assistant Professor
Department of Ophthalmology
The Johns Hopkins University
Krieger Eye Institute
Sinai Hospital of Baltimore
Baltimore, Maryland

Balwantray C. Chauhan, Ph.D.

Professor, Research Director, and
Chair in Vision Research
Department of Ophthalmology
Dalhousia University
Halifax, Nova Scotia
Canada

Abbot F. Clark, Ph.D.

Senior Director
Glaucoma Research
Alcon Laboratories
Fort Worth, Texas

Anne L. Coleman, M.D., Ph.D.

Associate Professor of Ophthalmology
Jules Stein Eye Institute
University of California at Los Angeles
Los Angeles, California

John Danias, M.D., Ph.D.

Assistant Professor
Department of Ophthalmology
Mount Sinai Medical Center
New York, New York

Robert J. Derick, M.D.

Clinical Associate Professor
Department of Ophthalmology
Ohio State University
Hilliard, Ohio

F. Jane Durcan, M.D.

Associate Professor Clinical
Department of Ophthalmology
Morga Eye Center
University of Utah
Salt Lake City, Utah

Albert O. Edwards, M.D., Ph.D.

Assistant Professor
Department of Ophthalmology
University of Texas Southwestern Medical Center
Dallas, TX

Babak Ellassi-Rad, M.D.

The Johns Hopkins Medical Center
Baltimore, Maryland

Thomas F. Freddo, O.D., Ph.D.

Professor of Ophthalmology, Physiology
and Anatomy
Department of Ophthalmology
Boston University School of Medicine
Boston, Massachusetts

Douglas E. Gaasterland, M.D.

Clinical Professor
Department of Ophthalmology
George Washington University
and Georgetown University
Washington, DC

Donna J. Gagliuso, M.D.

Assistant Professor
Department of Ophthalmology
Mount Sinai Medical Center
New York, New York

Ivan Goldberg M.B., B.S. (Syd),

F.R.A.N.Z.C.O., F.R.A.C.S.
Director, Glaucoma Services
Sydney Eye Hospital
Sydney, Australia

Weldon W. Haw, M.D.

Clinical Instructor
Stanford University, School of Medicine
Stanford, California

Miray Hamparian, M.D.

The Johns Hopkins Medical Center
Baltimore, Maryland

Eve J. Higginbotham, M.D.

Professor and Chair
Department of Ophthalmology
University of Maryland School of Medicine
Baltimore, Maryland

Yuri Ishihara, M.D.

Assistant Professor
Department of Ophthalmology
University of Texas Southwestern Medical Center
Dallas, Texas

Henry Jampel, M.D.

Assistant Professor of Ophthalmology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Chris Johnson, Ph.D.

Director of Diagnostic Research and Senior Scientist
Lions Anderson-Chenoweh-Ross Vision
Research Chair
Devers Eye Institute
Portland, Oregon

Douglas H. Johnson, M.D.

Professor of Ophthalmology
Mayo Clinic
Rochester, Minnesota

Elaine C. Johnson, Sc.D.

Assistant Professor
Casey Eye Institute
Department of Ophthalmology
Oregon Health and Science University
Portland, Oregon

Michael L. Klein, M.D.

Professor of Ophthalmology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

Allan E. Kolker, M.D.

Professor of Clinical Ophthalmology
Department of Ophthalmology
and Visual Sciences
Washington University
School of Medicine
St. Louis, Missouri

Scott Elliot LaBorwit, M.D.

Assistant Professor
Department of Ophthalmology
Wilmar Eye Clinic
Johns Hopkins Hospital
Baltimore, Maryland

Andreas Katsuya Lauer, M.D.

Assistant Professor of Ophthalmology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

David Lawlor, M.D.

Assistant Professor
Department of Surgery
University of Texas
Health Science Center at San Antonio
San Antonio, Texas

Mary G. Lynch, M.D.

Chief of Ophthalmology
Atlanta Veterans Affairs
Medical Center
Atlanta, Georgia

James E. Morgan, M.D., Ph.D., F.R.C.Ophth.

Senior Lecturer

Department of Ophthalmology
University Hospital of Wales
Cardiff
United Kingdom

John C. Morrison, M.D.

Director of the Glaucoma Service
The Fred P. Thompson Glaucoma Clinic
and Casey Eye Institute
And
Professor of Ophthalmology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

Mamdouh Nakla, M.D.

Visiting Assistant Professor
Jules Stein Eye Institute
Department of Ophthalmology
University of California at Los Angeles
Los Angeles, California

Gary D. Novack, Ph.D.

President
PharmaLogic Development, Inc.
San Rafael, California

Michael Passo, M.D.

Willamette Valley Medical Centre
McMinnville, Oregon

Christopher D. Pelzek, M.D.

Clinical Instructor
Department of Ophthalmology
University of Southern California
Los Angeles, California

Jody R. Piltz-Seymour, M.D.

Academic Professor of Ophthalmology
Scheie Eye Institute
University of Pennsylvania Health System
Philadelphia, Pennsylvania

Irvin P. Pollack, M.D.

Professor of Ophthalmology
The Johns Hopkins University
And
Emeritus Chief of Ophthalmology and Director
Krieger Eye Institute
Sinai Hospital of Baltimore
Baltimore, Maryland

John S. Pollack, M.D.

Assistant Professor of Ophthalmology
Rush Medical College

Illinois Retina Associates
Chicago, Illinois

Paul Rafuse, M.D.

Assistant Professor
Department of Ophthalmology
Dalhousie University
Halifax, Nova Scotia

Alan L. Robin, M.D.

Professor of Ophthalmology
University of Maryland
And
Associate Professor
School of Hygiene and Public Health
And
Associate Professor of Ophthalmology
The Johns Hopkins Medical Center
Baltimore, Maryland

James T. Rosenbaum, M.D.

Professor of Medicine Ophthalmology
and Cell Biology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

John R. Samples, M.D.

Professor of Ophthalmology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

Andrew P. Schachat, M.D.

Karl Hagen Professor of Ophthalmology
Wilmer Eye Institute
The Johns Hopkins University
Baltimore, Maryland

Janet B. Serle, M.D.

Associate Professor of Ophthalmology
Wilmer Eye Institute
Mount Sinai School of Medicine
Department of Ophthalmology
New York, New York

Paul A. Sidoti, M.D.

Associate Professor of Ophthalmology
Department of Ophthalmology
New York Medical College
The New York Eye and Ear Infirmary
New York, New York

Annapurna Singh, M.D., F.R.C.Ophth.

Department of Ophthalmology
Sehala Eye Institute
Philadelphia, Pennsylvania

Kuldev Singh, M.D.

Associate Professor of Ophthalmology
Director, Glaucoma Service
Department of Ophthalmology
Stanford University Medical Center
Stanford, California

Pait Teesalu, M.D., Ph.D.

Associate Professor
Department of Ophthalmology
University of Tartu
Estonia

Carol B. Toris, Ph.D.

Associate Professor
Department of Ophthalmology
University of Nebraska
Medical Center
Omaha, Nebraska

James Umlas, M.D.

Lexington Eye Associates
Lexington, Massachusetts

Martin B. Wax, M.D.

Professor
Department of Ophthalmology and Visual Sciences
Washington University School of Medicine
St. Louis, Missouri

Julia Whiteside-Michel, M.D.

Associate Professor of Ophthalmology
Case Western Reserve University
Cleveland, Ohio

Jacob Wilensky, M.D.

Professor of Ophthalmology
Director Glaucoma Service
University of Illinois at Chicago
Department of Ophthalmology
Chicago, Illinois

Mary K. Wirtz, Ph.D.

Associate Professor
Department of Ophthalmology
Casey Eye Institute
Oregon Health and Science University
Portland, Oregon

Preface

In recent decades, a rapid expansion in our understanding of the physiology, epidemiology, and genetics of glaucoma has brought about the development of new diagnostic and therapeutic techniques. As a result, it has become increasingly difficult for clinicians to assimilate this mass of information and apply it to the care of their patients.

A comprehensive understanding of this leading cause of blindness encourages the physician to be familiar with all of these basic and clinical science advances. This text is primarily intended to provide the resident and general clinician with a single volume, clinically-oriented source that covers the full spectrum of glaucoma problems, including the pathophysiology, epidemiology, and genetics of the many specific types of glaucoma. The glaucoma specialist, too, will also find the information provided by the international group of contributors to be authoritative, well documented and clearly presented.

To build and reinforce this understanding, we have taken the logical, time-honored approach of presenting first the pertinent, basic knowledge, followed by clinical disease entities and then their treatment. This is accomplished in 7 sections, beginning with the epidemiology and genetics. These two rapidly advancing disciplines provide an excellent framework for understanding the importance of glaucoma, both for society and the individual. They also provide important insights for understanding potential mechanisms and future therapy of the major forms of glaucoma that are discussed later in the text.

The next two sections discuss the basic and clinical sciences of two topics that are common to all forms of glaucoma: intraocular pressure and the optic nerve. In each section, we include the basic anatomy and physiology of the involved structures, as well as methods for their clinical evaluation. For the optic nerve section, this includes a discussion of glaucomatous optic neuropathy, and encompasses the clinical aspects of optic nerve damage as well as considerations of its likely mechanisms.

Specific chapters deal with new methods of analysis of the optic nerve head and nerve fiber layer, followed by a thorough discussion of perimetry and its application to glaucoma.

The next section considers the major categories of the clinical forms of glaucoma. Although this primarily follows an etiologic approach to disease classification, several major forms of glaucoma are each discussed in their own chapter, rather than under a broader heading. This is in keeping with our primary goal of presenting readily accessible information that is essential for clinical recognition and treatment. Each of these chapters considers the background of the entity, its pathogenesis, clinical diagnosis, and differential diagnosis, followed by medical and surgical management. The final 3 sections of the book discuss the medical, laser, and surgical methods commonly used in the management of all forms of glaucoma.

All chapters are introduced by an overview to prepare the reader for the content that is to follow. Highlight boxes emphasizing pearls, pitfalls, controversial points and items of special consideration are used to call the reader's attention to specific, important information. Tables are used throughout to provide a useful framework for understanding this information. This is to help the resident physician learn this material for the first time, and provide a quick reference useful to the busy clinical practitioner in need of a quick review.

Although this text is meant to be comprehensive, we have tried to present the most commonly encountered problems and the most important issues without providing an excess of information or detail. We recognize some information found in textbooks is quickly outdated by new information found in journals and presented at scientific meetings. This is certainly the case with the rapidly evolving fields of genetics and glaucoma therapy. Nevertheless, at the time of this publication the reader will find the information contained to be timely, current, and relevant.

Acknowledgments

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We are especially indebted to Doctors Bernard Becker and E. Michael Van Buskirk who, along with innumerable other mentors, provided us with our lifeline to ophthalmology and ophthalmic research.

SECTION I

EPIDEMIOLOGY AND GENETICS OF GLAUCOMA

EPIDEMIOLOGY OF GLAUCOMA

Anne L. Coleman, M.D.

Glaucoma is the second leading cause of blindness in the world.¹ As of the year 2000 66.8 million people are now estimated to have glaucoma, with 6.7 million bilaterally blind from this disease. Aside from its medical impact on the afflicted population, the total economic and social costs of glaucoma are virtually unknown.

In spite of many advances in the diagnosis and treatment of glaucoma, the fundamental causes of most glaucomas remain unknown. This hampers our ability to predict who will require treatment to prevent loss of vision. Generally, however, diseases do not occur at random; they instead present with specific patterns. The field

of epidemiology (Table 1–1) seeks to identify these patterns and gain insight into why certain individuals succumb to disease and others do not. This knowledge, in turn, helps us understand the mechanism of disease and guides screening and treatment toward specific populations and subpopulations.

PEARL... Epidemiology seeks to identify patterns of disease that can provide insights into why some people succumb to disease and others do not.

TABLE I-1 GLOSSARY OF TERMS COMMONLY USED IN EPIDEMIOLOGY

Terms	Definition
Population-based study	An investigation where research subjects are sampled from a well-defined set of individuals
Case-control study	An investigation contrasting individuals who have a disease or condition of interest ("cases") and individuals who do not ("controls")
Prevalence	The proportion of individuals who have a certain disease or trait at a given point in time
Incidence	The rate at which individuals develop the disease or trait over a specified time period
Demographic characteristics	Traits such as gender, age, and ethnicity that describe the mix of cases under study
Covariate	A trait or characteristic that is associated with the study outcome under investigation
Risk factor	A covariate associated with increased numbers of individuals having an adverse outcome under investigation
Risk	The probability or expected rate of developing the disease under investigation
Relative risk	A measure of the proportional increase in the risk of the disease between one group and another
Odds	$p/(1 - p)$, where p denotes the probability of an event
Odds ratio	The ratio of the odds of occurrence of the disease in one group to the odds of occurrence in another group, often used as an estimate of relative risk
Adjusted odds ratio	An odds ratio estimated from a statistical model that assesses the relationship between a risk factor of interest and a study outcome while controlling for the effects of the other covariates

When glaucoma is broadly classified into primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG), our understanding of the epidemiology of glaucoma draws from both global and regional experiences. The distinct geographic tendencies of these entities throughout the world help guide public health resources dedicated to the diagnosis and treatment of glaucoma. This knowledge also helps individual practitioners as they evaluate and treat ever increasing numbers of patients from diverse ethnic backgrounds. These epidemiological evaluations rely on standardized definitions of both forms of glaucoma. This allows investigators to perform careful comparisons among different studies and draw meaningful conclusions.

Studies of the specific patterns of these diseases, or risk factors, are derived mostly from Europe, the United States, and Australia. Because PACG is less common in these regions, our understanding of its risk factors is limited, although some have been identified, such as age, gender, refractive error, and family history.

In contrast, POAG has been widely studied. Many population-based studies and clinical series now exist; they provide accurate information on the prevalence of this condition and its relationship to several risk factors, which, in turn, sheds light on the possible mechanisms of this disease. Among these risk factors, intraocular pressure (IOP), ethnicity, and age are well established. Diabetes mellitus, systemic hypertension, myopia, and migraine headaches seem more controversial.

PUBLIC HEALTH IMPACT OF GLAUCOMA

In the United States, were estimated to be 130,540 people blind from primary glaucoma in the year 2000.² In Olmsted County, Minnesota, 9% of subjects aged 66 years when diagnosed with glaucomatous optic nerve damage or visual field loss were bilaterally blind at the 20-year follow-up, in spite of receiving treatment.³ Although it is easy to imagine the difficulties associated with living in today's society with vision less than 20/400 or 3/60 in the better eye (World Health Organization's criteria for blindness), many people do not understand the impact that loss of peripheral vision, depth perception, and contrast sensitivity can have on an individual's life prior to blindness. Topical eye medications and glaucomatous visual field loss are associated with an increased risk of falls and fractures in the elderly.⁴ In addition, a diagnosis of glaucoma is an independent risk factor for injurious car crashes in subjects 55 to 87 years of age.⁵

Because the visual loss and medications associated with glaucoma affect the activities of daily living,^{6–10} the economic impact of glaucoma on society is essentially unknown. Although we can measure the cost of medically treating glaucoma,¹¹ the costs of visual impairment and blindness are much more difficult to estimate.

Glaucoma is not a single disease but many. It is often categorized into PACG, secondary angle-closure glaucoma, POAG, secondary open-angle glaucoma, congenital glaucoma, and juvenile glaucoma.

As Figure 1–1 shows, the most common type of glaucoma in one region of the world may differ from that in another region. PACG is more common in Asia, whereas POAG is more evenly distributed throughout the world.¹ In the United States, Europe, and Australia, 75 to 95% of glaucoma in Caucasians is POAG,^{1,12} whereas PACG accounts for 70 to 90% of glaucoma in China and India.^{12–14} Most glaucoma in Japan is POAG, which includes normal-tension glaucoma.¹⁵ Unfortunately, very little is known about which type of glaucoma is most prevalent in Africa. However, this is most likely POAG because PACG is rare in African Americans.¹⁶ In South America and the Near East, clinical records suggest that POAG is the most common form of glaucoma, even though PACG is more prevalent there than in Caucasians in both the United States and Europe.¹

This global perspective strongly suggests that people of certain ethnic groups are more likely to have either PACG or POAG. This helps the practitioner diagnose and treat the individual glaucoma patient. From a public health perspective, understanding the epidemiology of PACG and POAG helps us determine why certain individuals are more likely to develop these conditions, and can improve the screening, treatment, and prevention of blindness.

PRIMARY ANGLE-CLOSURE GLAUCOMA (SEE ALSO CHAPTER 16)

DEFINITION OF PRIMARY ANGLE-CLOSURE GLAUCOMA

The 1996 American Academy of Ophthalmology Preferred Practice Pattern defines PACG as "appositional or synechial closure of the anterior chamber angle caused by relative pupillary block in the absence of other causes of angle closure."¹⁷ Because PACG is a relatively rare disease in Europe, the United States, and Australia, very little is known of its epidemiology. In addition, the diagnosis of PACG depends on gonioscopy. However, there is no universally accepted gonioscopic definition of angle closure, which complicates comparison of population-based studies on this condition.

RISK FACTORS FOR PRIMARY ANGLE-CLOSURE GLAUCOMA

Ethnicity

Several population-based studies have found that individuals of Eskimo or Chinese descent are at increased risk of PACG. The prevalence of PACG is 20 to 40 times higher in Eskimos than in Caucasians.¹² In addition,



FIGURE 1-1 Geographic distribution of primary angle-closure glaucoma (red) and primary open-angle glaucoma (POAG) (green) throughout the world. Although detailed studies on the epidemiology of glaucoma in South America and Africa are currently lacking, indirect evidence suggests that POAG is most common in these regions. Unshaded areas indicate insufficient study.

a population-based survey from Singapore associated a history of Chinese descent with a greater risk for PACG.¹⁸ The increased risk in Eskimos probably results from a smaller eye size and more crowded anterior chamber.¹⁹ With the exception of a smaller corneal curvature, however, the axial length and anterior chamber depth of Taiwanese and Caucasian eyes are remarkably similar.²⁰

Age

Older patients are more likely to develop PACG. This increased risk probably results from steady growth of the crystalline lens throughout life.^{21,22} In Eskimos, Chinese, and Caucasians, the anterior chamber shallows and the angles become progressively narrower as the lens thickens.^{19,23–26} Because this disease is more prevalent within and beyond the fifth decade of life, it is recommended that screening for PACG start at age 40.¹²

Gender

Several population-based surveys suggest that women are at increased risk for PACG.^{12,18,27} Whether this is because women have smaller eyes and anterior chambers than men is uncertain. In Eskimos, women have more shallow anterior chambers than men.¹⁹ In Chinese and Caucasians, however, these differences are not enough to explain why women are more likely to develop PACG than men.

Refractive Error

Among Caucasians, hyperopia is associated with PACG.²⁷ In a population-based survey in Western Cape, South Africa, individuals of Southeast Asian descent with hyperopia were more likely to have PACG.²⁸ A comparison of the refractive errors between subjects in the Baltimore Eye Survey and a small population-based sample in Taiwan, however, showed that Caucasians were more likely to have refractive errors of +2.00 diopters or more.²⁰ In spite of this, PACG is more common in Chinese than in Caucasians.

Positive Family History

A family history seems to be a strong risk factor for PACG across several ethnic groups. One to 12% of first-degree relatives of Caucasians with PACG can develop PACG.¹² In Eskimos, the prevalence of PACG in first-degree relatives of patients with this disorder may be 3.5 times higher than in the general population.¹⁹ A population-based survey in China showed that any family history of glaucoma increased the risk of PACG sixfold.²⁵

Environmental Factors

Some population-based studies have reported associations of PACG attacks with the weather, such as the number of hours of sunshine and the daily temperature. A study in Singapore reported more attacks on hotter

days, and suggested that angle-closure attacks are more likely on days with more hours of direct sunshine.¹⁸ In Israel,²⁹ PACG attacks occurred more frequently in the summer and winter. On the other hand, in Finland such attacks were more frequent in autumn and winter, when there is less sun exposure.³⁰ The association of acute PACG attacks with the number of sunspots is similarly controversial.¹⁸ Currently, we do not understand the exact role of the weather in acute PACG.

PRIMARY OPEN-ANGLE GLAUCOMA

(SEE ALSO CHAPTER 15)

DEFINITION OF PRIMARY OPEN-ANGLE GLAUCOMA

The 1996 American Academy of Ophthalmology Preferred Practice Pattern defines POAG as a “chronic, generally bilateral and often asymmetrical disease, which is characterized (in at least one eye) by all of the following”:

1. Evidence of glaucomatous optic nerve damage from either or both of the following:
 - i. The appearance of the disc or retinal nerve fiber layers (e.g., thinning or notching of the disc rim, progressive change, nerve fiber layer defects)
 - ii. The presence of characteristic abnormalities in the visual field (e.g., arcuate defect, nasal step, paracentral scotoma, generalized depression) in the absence of other causes or explanations
2. Adult onset
3. Open, normal-appearing anterior chamber angles
4. Absence of known other (e.g., secondary) causes of open angle glaucoma³¹

Depending on the definition of POAG, the prevalence of this disease in population-based studies ranges from 0.4 to 8.8%^{15,23,32–42} (Table 1–2). The majority of these studies used the appearance of both optic nerve head and visual field as part of the diagnostic criteria.^{15,23,32–42} In the Blue Mountains Eye Study,⁴¹ there was a prevalence of 5.6% when optic nerve damage alone was deemed sufficient to satisfy the diagnostic criteria for POAG. However, including both optic nerve head and automated visual field criteria decreased the prevalence by more than half, to 2.4%.

RISK FACTORS FOR OPEN-ANGLE GLAUCOMA

The risk factors for POAG generally break down into demographic and clinical categories. However, IOP, which may be closely connected to the mechanism of POAG, deserves special attention.

Intraocular Pressure

The American Academy of Ophthalmology definition³¹ of POAG does not include IOP. Several population-based

studies (Table 1–2) include elevated IOP in their diagnosis of POAG. In an editorial in the *American Journal of Ophthalmology*, Sommer⁴³ discussed how IOP may be a risk factor, even when the IOP is only 16 mm Hg. The prevalence of POAG in both whites and African Americans progressively increases with higher levels of screening IOP (Fig. 1–2; Table 1–3). In addition, people can satisfy criteria for POAG even when the IOP is less than 18 mm Hg. In the Baltimore Eye Survey, 47 out of 3571 eyes with an IOP of 16 to 18 mmHg (0.01%) met the definition for POAG.⁴⁴ These statistical associations are all consistent with IOP as a risk factor for POAG. However, they do not prove that IOP causes POAG in all cases.

PEARL... Epidemiology can determine the role of intraocular pressure in glaucoma by inference, but cannot prove it.

Such proof of causation can be inferred but not directly observed. Even randomized studies must rely on the inference that chance alone does not explain their results. Epidemiological studies, which lack the standardization of randomized trials, require even stronger assumptions. One approach to this problem draws on the experience of the 1962 Advisory Committee to the Surgeon General on smoking and health.⁴⁵ From this, we can determine several lines of evidence suggesting that IOP is a causal risk factor for POAG. This evidence satisfies the following criteria:

1. *Consistency of association.* The population-based studies in Wales,³² Framingham,²³ Baltimore,³⁵ Beaver Dam,³⁶ Barbados,³⁹ and Blue Mountains⁴¹ all showed a consistent association between IOP level and POAG.
2. *Strength of association.* The Baltimore Eye Study⁴⁴ reported that the strength of this association increased with progressively higher IOPs. Compared to eyes with screening IOP less than or equal to 15 mm Hg, the relative risk of POAG in eyes with IOPs of 22 to 29 was 12.8, and 39.0 for eyes with screening IOPs of 30 to 34⁴⁴ (Table 1–3).
3. *Specificity of association.* This refers to the extent that a cause can be identified as leading to an effect to the exclusion of other factors. For example, it seems plausible that elevated IOP by itself could induce POAG given that elevated IOP may cause vascular ischemia, decreased perfusion of the optic nerve head, mechanical compression of the lamina cribrosa, and decreased axoplasmic flow. All of these events may be important features of glaucomatous optic nerve damage.
4. *Temporal relationship of association.* This means that the cause precedes the disease. This clearly occurs in the nonhuman primate model of glaucoma⁴⁶ and in human eyes with acute-angle closure glaucoma, where elevated IOP causes glaucomatous optic nerve damage. Further support comes from the report of Kass and coauthors⁴⁷ that lowering IOP in ocular hypertensives

TABLE I-2 SELECTED POPULATION-BASED STUDIES ON THE PREVALENCE OF PRIMARY OPEN-ANGLE GLAUCOMA

<i>Study Location</i>	<i>Diagnostic Criteria for Glaucoma</i>	<i>Age Group (years)</i>	<i>Race</i>	<i>Number of Subjects (% of eligible)</i>	<i>Mean Intraocular Pressure (mm Hg)</i>	<i>Tonometer</i>	<i>Prevalence</i>
Ferndale, UK ³²	ONH + Goldmann VF defect	40–75	white	4231 (92%)	15.1 16.3	Schiotz, Applanation	0.4%
Jamaica ³³	ONH + Goldmann VF defect	≥35	black	574	16.6 (all eyes)	Applanation	1.4%
Framingham, MA ²³	ONH + Goldmann VF defect	52–85	white	2675 (67%)	16.5 (all eyes)	Applanation	2.2%
Sweden ³⁴	ONH + VF defect	≥50	white				Entire population
Japan ¹⁵	ONH + VF defect	≥40	Asian	8126 (51%)	13.2 (nonglaucoma)	Non-contact	2.6%
Baltimore, MD ³⁵	ONH and/or Goldmann VF defect	≥40	white	2913 (79%)	17.2 (nonglaucoma)	Applanation	1.3%
Baltimore, MD ³⁵	ONH and/or Goldmann VF defect	≥40	black	2395 (79%)	16.0 (nonglaucoma)	Applanation	4.7%
Beaver Dam, WI ³⁶	IOP, ONH and/or automated VF defect	43–86	white	4926 (83%)	15.4 (all eyes)	Applanation	0.7%
Roscommon, Ireland ³⁷	ONH + automated VF defect	≥50	white	2186 (99.5%)	14–15 (nonglaucoma)	Applanation	1.9%
Rotterdam, The Netherlands ³⁸	ONH or IOP + Goldmann VF defect	≥55	white	3062 (71%)	14.6 (all eyes)	Applanation	1.1%
Barbados, West Indies ³⁹	ONH + automated VF defect	40–84	black	4709 (84%)	18.7 (all eyes)	Applanation	6.6%
St. Lucia, West Indies ⁴⁰	ONH and/or automated VF defect	30–86	black	1679 (87%)	17.7 (all eyes)	Applanation	8.8%
Blue Mountains, Australia ⁴¹	ONH + automated VF defect	49–97	white	3654 (82%)	16.1 (all eyes)	Applanation	2.4%
Melbourne, Australia ⁴²	IOP + family history + ONH + VF defect	≥40	white	3271 (83%)	14.3 (all eyes)		1.7%

ONH, optic nerve head appearance consistent with glaucoma; VF, visual field defect consistent with glaucoma.

TABLE I-3 PREVALENCE OF PRIMARY OPEN-ANGLE GLAUCOMA IN RELATION TO SCREENING INTRAOCULAR PRESSURE

<i>Intraocular Pressure (mm Hg)</i>	<i>Prevalence (%) (±SEM)</i>	<i>Relative Risk</i>
≤15	0.65 (±0.13)	1.0
16–18	1.31 (±0.19)	2.0
19–21	1.82 (±0.28)	2.6
22–24	8.30 (±1.31)	12.8
25–29	8.33 (±1.78)	12.8
30–34	25.37 (±5.32)	39.0
≥35	28.09 (±9.16)	40.1

(Adapted, with permission, from *Arch Ophthalmol* 1991;109:1092. Copyright, 1991, American Medical Association.)

reduces their risk of developing POAG. This observation has recently been strengthened by results of the Ocular Hypertension Treatment Study,⁴⁸ which showed that lowering IOP by 20% in eyes with elevated IOP reduced the probability of developing POAG to 4.4% after 5 years. This was significantly less ($P < .0001$) than that seen in the untreated group.⁴⁸

5. Coherence of the association. This means that the interpretation of causality does not conflict with what is known about the natural history and biology of the disease. Thus the treatment of glaucoma, to lower IOP to a level (the target IOP) where there is no further optic nerve damage or visual field loss,³¹ is coherent with a causal role for IOP.

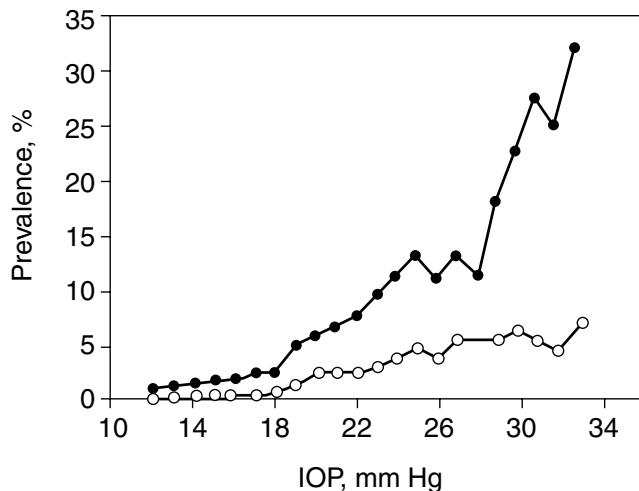


FIGURE 1-2 Prevalence of primary open-angle glaucoma in eyes in relation to their screening intraocular pressure, comparing white subjects (open circles) to black subjects (closed circles). (Reproduced with permission from *Arch Ophthalmol* 1991;109:1092. Copyright 1991, American Medical Association.)

Today, epidemiologists do not use a checklist of criteria to infer causation, but instead evaluate competing causal theories by how well they conform to crucial observations. In this manner, the observation that eyes with a higher screening IOP have a larger relative risk for POAG⁴⁴ supports the possibility that IOP can cause POAG. Similarly, subjects with asymmetric glaucomatous optic nerve damage usually have the larger cup in the eye with the higher IOPs.^{49,50} Even more support comes from the Collaborative Normal-Tension Glaucoma Study, which found that reducing IOP by at least 30% significantly decreases vision loss, compared with control eyes without similar IOP reductions.⁵¹

CONTROVERSY

Although the role of intraocular pressure in the pathogenesis of glaucoma has been controversial, it remains an important risk factor for this disease.

Demographic Risk Factors for POAG

Age

Every population-based study has shown a statistical association between age and the prevalence of POAG.^{15,23,32-42} As an individual gets older, the risk for POAG increases. In the Baltimore Eye Survey,³⁵ the prevalence of glaucoma in whites was 3.5 times higher for individuals 70 to 79 years old (2.89%) as compared with those in their 40s (0.82%). In African Americans, the corresponding ratio was 7.4. Although age is clearly a risk factor for POAG, glaucoma can still occur in individuals younger than 40.

Currently, we do not know why POAG is more prevalent in the elderly. Because nearly all chronic diseases are more common in older individuals, however, age may be a proxy for any of a number of possible underlying genetic, biological, or environmental factors.

Gender

Population-based studies disagree on the association between gender and POAG. Although males had higher rates of POAG in Framingham²³ and Barbados,³⁹ studies from Sweden,³⁴ St. Lucia,⁴⁰ and the Blue Mountains⁴¹ all reported higher rates in females. Both results were statistically significant. However, studies in Wales,³² Baltimore,³⁵ Beaver Dam,³⁶ and Melbourne⁴² found no such statistical associations. Gender is not usually considered a risk factor for POAG.

Ethnicity

Several population-based studies show that individuals of African heritage have an increased risk of developing POAG. In the Baltimore Eye Survey, African Americans were 3.7 times more likely to have glaucoma than whites, with an age-adjusted prevalence rate of 4.74% for African Americans and 1.29% for whites.³⁵ Although in Jamaica the estimated prevalence of POAG in blacks aged 35 years or older was only 1.4%,³³ rates in other parts of the Caribbean were even higher than those observed in Baltimore, 8.8% (ages over 30) in St. Lucia⁴⁰ and 6.6% (ages 40 to 84) in Barbados.⁴³ The prevalence of open angle glaucoma in Hispanic adults living in Arizona is intermediate between the reported values for whites and African Americans. It increased from 0.5% in Hispanic individuals age 41 to 49 years to 12.63% in those 80 years and older.^{51a}

The cause of this higher prevalence of glaucoma in those of African or Hispanic origin is currently unknown. Although African Americans have larger cup-to-disc ratios than whites,⁵² they also have larger discs and more nerve fibers. Some investigators theorize that the increased disc area is associated with increased mechanical stress, putting the African American optic nerve at greater risk for glaucomatous damage.⁵³ In support of this hypothesis, the Baltimore Eye Survey showed that the prevalence of POAG in African Americans compared with whites was higher at each specific level of IOP, even though they had a similar distribution of IOPs⁴⁴ (see Fig. 1-2).

PEARL... Optic nerve characteristics, such as disc hemorrhage or asymmetric cupping, are not considered risk factors for glaucoma because they are part of the definition of glaucomatous optic nerve damage.

Clinical or Other Potential Risk Factors

Positive Family History and/or "Glaucoma Genes"

Several population-based studies support an association between a positive family history for glaucoma and POAG. The Baltimore Eye Survey revealed an age-race adjusted odds ratio of 2.85 for an association between POAG and a history of glaucoma among first-degree relatives.⁵⁴ This association was strongest in siblings (age-adjusted odds ratio = 3.69) and weakest in the children of study subjects (age-adjusted odds ratio = 1.12). In the Barbados Eye Study,⁵⁵ previously undiagnosed subjects were more likely to develop glaucoma if they had a history of glaucoma in one or more siblings (odds ratio = 4.5). The population-based familial aggregation study in Rotterdam⁵⁶ showed that the lifetime risk of glaucoma in siblings and offspring of glaucoma patients was 9.2 times higher than in those of controls. Chapter 2 discusses the genetics of POAG and other forms of glaucoma.

PEARL... Intraocular pressure, age, African heritage, and family history are well-established risk factors for glaucoma.

Adult-Onset Diabetes Mellitus

Several case-control studies demonstrate statistical associations between diabetes and POAG.⁵⁷⁻⁵⁹ This may, however, result from selection bias. Because diabetics often undergo detailed eye examinations to rule out diabetic retinopathy, they have a greater opportunity to be diagnosed with POAG than nondiabetics. The Baltimore Eye Survey⁶⁰ found no statistical association between diabetes mellitus and POAG (age-adjusted odds ratio of 1.03). However, a positive association did exist in individuals whose POAG had been diagnosed prior to the study, supporting the possibility that selection bias did influence the case-control studies. On the other hand, both the Beaver Dam⁶¹ and the Blue Mountains⁶² studies found that the odds of a diabetic having POAG were two times greater than those of a nondiabetic. In the Blue Mountains Eye Study,⁶² the association was even greater in individuals with previously diagnosed glaucoma.

Although diabetes mellitus may or may not be a risk factor for POAG, diabetics tend to have higher IOPs than nondiabetics, and this may explain a greater prevalence of POAG in this disease. However, the relationship between diabetes mellitus and POAG persisted in the Blue Mountains Eye Study⁶² even after controlling for IOP in the data analysis. This association could also result from the effect of diabetes on the small vessels of the eye and the optic nerve head, producing an increased susceptibility to IOP.

Systemic Hypertension

Case-control studies^{57,63} and population-based surveys provide mixed results on the statistical association between systemic hypertension and POAG. Although the Barbados⁶⁴ and Baltimore⁶⁵ studies did not find such an association, the study in Rotterdam⁶⁶ did. For example, the Baltimore Eye Survey⁶⁵ showed that systemic hypertension (defined as systolic and diastolic blood pressures greater than 160 mm Hg and 95 mm Hg, respectively, or current use of antihypertensive medications) was not a risk factor for glaucoma. On the other hand, this study did find that individuals with diastolic perfusion pressure (diastolic blood pressure minus IOP) less than 30 mm Hg were six times more likely to have POAG than those with a perfusion pressure of 50 mm Hg or more. The Barbados Eye Study⁶⁴ reported a similar result (odds ratio = 3.29).

This association between diastolic perfusion pressure and POAG could result from autoregulation of optic nerve head blood vessels, which may protect the optic nerve head as long as perfusion pressure remains above 50 mm Hg. Below this level, due to either decreased blood pressure or elevated IOP, the autoregulatory response may degrade and increase the susceptibility of the optic nerve head to glaucomatous damage.⁶⁷

Myopia

As with diabetes mellitus, there is concern that selection bias may label myopia a risk factor for POAG. Because myopes have more problems with their vision and need glasses, whereas emmetropes do not, they have greater opportunity to be diagnosed with POAG. However, one case-control study⁵⁷ reported that patients with POAG were twice as likely to have myopia than controls. Perkins and Phelps⁶⁸ reported that 27.4% of subjects with POAG were myopic versus 6.9% of the normal population. In addition, population-based studies in Casteldaccia⁶⁹ and the Blue Mountains of Australia^{69a} showed a statistical association between POAG and myopia greater than or equal to 1.5 diopters.

Although it is still uncertain whether myopia is a risk factor for POAG, elevated IOP is statistically associated with myopia.⁷⁰ Alternatively, the anatomy of the myopic disc may predispose it to glaucomatous optic nerve damage.⁷¹

CONTROVERSY

Investigators disagree on whether diabetes mellitus, systemic hypertension, myopia, and migraines are risk factors for primary open-angle glaucoma.

Migraines

Several investigators have suggested that migraine headaches, or a vasospastic tendency, are also a risk fac-

tor for POAG. In one case-control study, Phelps and Corbett⁷² found a statistically significant relationship between headaches in low-pressure glaucoma subjects aged 70 years or older compared with controls. However, another study⁷³ found no such association. Neither the Beaver Dam Eye Study⁷⁴ nor the Blue Mountains Eye Study⁷⁵ found a significant association between migraine headaches and POAG overall. However, the latter did show that, in the 70- to 79-year age group, the odds of a typical migraine were 2.48 times greater in subjects with glaucoma than in those without glaucoma. Although the association between migraines and glaucoma remains controversial, vasospasm can theoretically encourage optic nerve damage by decreasing blood flow to the optic nerve head.

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GLAUCOMA GENETICS

Mary K. Wirtz, Ph.D. and John R. Samples, M.D.

The recent explosion in our knowledge of the genetic basis of disease brings promise for understanding the causes of glaucoma and improving its diagnosis and treatment. Mapping techniques based on large families with well-defined forms of glaucoma have localized several genes related to adult primary open-angle glaucoma (POAG) and congenital glaucoma, and identified several genes related to specific types of glaucoma. By understanding the functions of the affected genes, these mapping results may provide important clues to the mechanism of disease. This is already being suggested for the trabecular meshwork-induced glucocorticoid response/myocilin (*TIGR/MYOC*) gene.

This knowledge allows early diagnosis of specific forms of glaucoma, which in turn allows targeting of individuals at high risk of developing optic nerve damage and early, aggressive treatment with currently available glaucoma therapy. Eventually this genetic information will lead to the development of new drugs to bypass the consequence of the identified gene defect, thereby allowing specific therapy of the cause of glaucoma in individual patients as determined by their genotype.

Ultimately, gene therapy, using either replacement of deoxyribonucleic acid (DNA), modification of messenger ribonucleic acid (mRNA), or replacement of the defective protein, may provide long-term relief. Several potential approaches to such therapy are now in development and may be targeted at either the trabecular meshwork or the ciliary body. These may use either viral vectors or non-vector approaches, such as liposomes, ribozymes, and antisense therapy. As these therapies evolve, specific gene therapy can be used to replace or circumvent the defective glaucoma gene before visual loss has occurred.

BACKGROUND

Albrecht von Graefe was one of the first clinician scientists to observe that many cases of open-angle glaucoma occurred with a familial tendency.¹ In 1949, Posner and

Schlossman commented, "To the patient and to his family, it is of the utmost importance to know whether his disease will follow a mild course or will lead to blindness.... The genetic approach is helpful in predicting the probable course in a case of glaucoma."²

Nearly 20 years later, Kass and Becker observed strong correlations between family history and glaucoma, particularly intraocular pressure (IOP), cup-to-disc ratios, and glucocorticoid responsiveness.³ Based on these observations, they suggested that the best and most effective method of glaucoma detection would be to check parents, siblings, and children of glaucoma patients for the disease.

Further understanding of the genetics of glaucoma resulted from efforts to understand the nature of the glucocorticoid-induced elevation in IOP and the realization that other factors, some of them environmental, are also involved in glaucoma. In the last decade, using powerful molecular genetics techniques, investigators have successfully mapped several glaucoma genes, which may one day provide important clues to the origin, diagnosis, and treatment of this complex disease.

GLUCOCORTICOID RESPONSE

Analyzing the glucocorticoid response in glaucoma patients and their families was a pioneering step toward understanding the molecular basis of glaucoma. Becker and Hahn⁴ and later Armaly⁵ found that glucocorticoid treatment produced elevated intraocular pressures more often in glaucoma patients than in normal individuals. Testing of family members showed that this response was inherited as an autosomal recessive trait.

Polansky hypothesized that trabecular meshwork glucocorticoid response genes could be glaucoma candidate genes, mutations of which can produce the disease.⁶ He identified the TIGR protein, which is produced by trabecular meshwork cells. The timing of this production coincided with the elevation in IOP following exposure

to glucocorticoids.⁶ Mutations in TIGR were later identified in juvenile glaucoma families and found to affect ~3% of the general glaucoma population (see the following text).⁷

These observations support Becker and Armaly's hypothesis that the glucocorticoid response is associated with glaucoma. However, although the glucocorticoid response is inherited as an autosomal recessive trait, glaucoma in the juvenile glaucoma families is autosomal dominant. Additional factors are probably also involved in this disease.

ENVIRONMENTAL FACTORS

Evidence that environmental factors can also affect glaucoma arises from twin studies: analysis of the season of birth of glaucoma patients and light exposure in animal models.^{8–11} Theoretically, if glaucoma is genetically determined, identical twins should share this trait more often than fraternal twins. In the Finnish Twin Cohort Study, three of the 29 monozygotic twin pairs were concordant for POAG, compared with one of 79 dizygotic twin pairs.¹⁰ Although a higher percentage of monozygotic twins were concordant for glaucoma, most were not. These data suggest that, although genetic factors do contribute to the etiology of glaucoma, the development of the disease in each individual must also depend on other factors, such as environmental influences and multifactorial inheritance.

Along these lines, Weale observed that patients born in the British Isles between the months of April and June have a higher preponderance of glaucoma, implying that the season of birth may affect a predisposition to glaucoma.⁹ Studies in chicks suggest that long hours of light exposure may increase the risk for glaucoma.¹¹

MAJOR GLAUCOMA GENES

In the mid-1990s, *GLC1A*, a form of juvenile open-angle glaucoma, was mapped to chromosome 1.⁷ This was soon followed by the mapping of five POAG genes.^{12–16} However, the "nature versus nurture" argument continues. Although a major gene definitely causes glaucoma in specific individuals, the proportion of all glaucoma patients affected by one major gene or another is currently unknown. Most glaucoma cases probably result from a complex interaction of genetic and environmental influences.

GLAUCOMA GENE CLASSIFICATION

Studies of DNA from families with hereditary glaucoma show that glaucoma loci can be located, or "mapped," to specific sites on a human chromosome. Five open-angle, two congenital, and one juvenile glaucoma loci are currently known (Table 2–1), along with several syndromes

known to be related to specific forms of glaucoma. Additional discoveries are soon likely and will be designated according to the following standard nomenclature.

The Human Genome Organization/Genome Database (HUGO/GDC) now uses "*GLC*" as the general symbol for the glaucoma genes. The numbers 1, 2, and 3 represent open-angle, angle-closure, and congenital glaucoma, respectively. These are followed by letters, which are assigned in alphabetical order as each new gene is mapped in each subgroup. For example, *GLC1F* is the fifth POAG locus to be described. This information is constantly expanding because several new glaucoma loci are mapped every year.

DETECTION AND LOCATION OF GLAUCOMA GENES

Mapping new glaucoma genes requires close collaborations between molecular geneticists and clinicians with access to large families containing at least five to 10 affected members. The first step relies upon accurately identifying patients with positive family histories for glaucoma and making firm diagnoses of the affected family members, using well-defined clinical definitions of the disease.

PEARL... Mapping new glaucoma genes requires close collaborations between the clinician and the molecular geneticist.

Tissue samples, usually blood or buccal mucosa swabs, are collected from each participating family member. The laboratory then amplifies the DNA from these samples using polymerase chain reaction (PCR) techniques, and, with microsatellite marker primers, determines the location of any gene common to the family members with glaucoma.

Figure 2–1A,B illustrates the general approach of the microsatellite marking technique. Every individual carries two copies of each chromosome, one derived from each parent. For this example, the mother has the AB allele and the father the BD allele. Through random segregation, the children can inherit four different possible genotypes from this mating, AB, BD, BB, or AD. Microsatellites (di-, tri- or tetranucleotide repeats) are dispersed randomly throughout this genomic material. These microsatellites are randomly segregated and transmitted from one generation to the next. In the laboratory, these microsatellite products are amplified by PCR and separated by size on sequencing gels, which then display the genotype of each individual.

If all family members with glaucoma share similar satellite markers in a specific chromosomal region, the glaucoma gene is more likely to be in this site. Linkage

TABLE 2-1 CURRENTLY MAPPED GLAUCOMA GENES

Locus	Location (Reference)	Phenotype	Inheritance	Age at Onset	Gene
GLC1A	1q23-q25 (7)	JOAG	Dominant	5–45	TIGR/MYOC
GLC1B	2cen-q13 (16)	POAG	Dominant	>40	—
GLC1C	3q21-24 (12)	POAG	Dominant	56 (38–80)	—
GLC1D	8q23 (15)	POAG	Dominant	>30	—
GLC1E	10P15-14 (14, 24)	POAG	Dominant	44 (23–65)	OPTN
GLC1F	7q35 (13)	POAG	Dominant	53 (22–70)	—
GLC3A	2p21 (30, 32)	Congenital	Recessive	<3	CYP1B1
GLC3B	1p36 (29)	Congenital	Recessive	<3	—
NNOS	11 (27)	Angle-closure	Dominant	28.3 (7–77)	—
RIEG1	4q25 (33)	Rieger's syndrome	Dominant	<3	PITX2
RIEG2	13q14 (57)	Rieger's syndrome	Dominant	<3	—
IRID1	6p25 (33)	Iridogoniodysgenesis	Dominant	<3	FKHL7
	7q35 (24)	Pigment dispersion	Dominant	20s	—
NPS	9q34 (34)	Nail-patella syndrome	Dominant	32 (18–41)	LMX1B

POAG, primary open-angle glaucoma; JOAG, juvenile open-angle glaucoma.

analysis calculates this probability as the log of the ratio of the likelihood that the glaucoma gene and the marker are linked over the likelihood that they are not linked. If the logarithm of this ratio, the lod score, is over 3, the likelihood is 1000:1 that the two loci are linked. This score is generally considered a positive result.

These techniques have revealed the probable locations of genes representing POAG, congenital glaucoma, and angle-closure glaucoma. In a few instances, specific glaucoma-associated genes are now known, which may provide insights into mechanisms of these diseases.

OPEN-ANGLE GLAUCOMA GENE (GLC1)

GLC1A, the first open-angle glaucoma gene identified, was initially mapped in a large juvenile glaucoma family to chromosome 1.^{17–20} Mutations in this gene, which are suspected as responsible for *GLC1A*,^{7,21} produce a protein that is also induced in trabecular meshwork cells by treatment with dexamethasone⁶ (*TIGR*). Because this protein has also been identified as myocilin (*MYOC*)²² the

HUGO/GDC nomenclature committee proposed that the gene symbol be *TIGR/MYOC* for the *TIGR/myocilin* gene.

Mutations in *TIGR/MYOC* are not limited to juvenile glaucoma and have been reported in 3% of individuals with adult-onset POAG.⁷ Since corticosteroids may increase IOP in a high percentage of glaucoma patients,²³ Polansky et al⁶ have hypothesized that a *TIGR/MYOC*-related protein could be responsible for outflow obstruction in glaucoma. However, *TIGR/MYOC* protein is also expressed in the retina, skeletal muscle, and fetal heart.²¹ Therefore, the precise relationship between *TIGR/MYOC* gene corticosteroid-response glaucoma, and POAG remains uncertain.

CONTROVERSY

Despite the strong association of *TIGR/MYOC* with the corticosteroid response, the precise role of its protein in steroid-induced glaucoma and POAG is currently unknown.

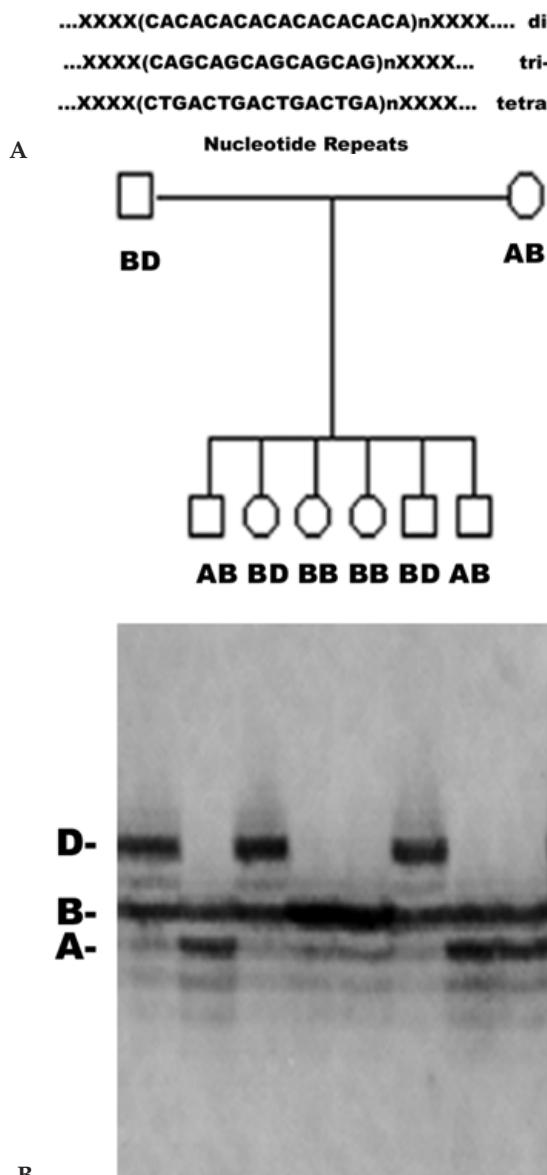


FIGURE 2-1 Pictogram of nucleotide repeats and pedigree demonstrating the inheritance of microsatellite marker alleles. (A) Nucleotide repeats can be composed of di-repeats such as CA, tri-repeats such as CAG, or tetra-repeats such as CTGA. The number of each repeat, inherited from one generation to the next, will vary from person to person. (B) Pedigree and gel showing the genotypes of six siblings and their parents. Gel lanes are aligned directly below the corresponding family member in the pedigree. A,B, and D represent the three alleles in this family.

Other researchers have identified two loci for normal tension forms of POAG. *GLC1B* maps to chromosome 2,¹⁶ whereas *GLC1E* maps to chromosome 10.¹⁴ Because the majority of individuals with the *GLC1B* or the *GLC1E* gene have normal-tension glaucoma, mutations of *GLC1B* and *GLC1E* may render the optic nerve abnormally sensitive to IOP, or facilitate optic nerve damage independent of IOP. Mutations in *OPTN*, encoding the optinuerin protein, have recently been identified in *GLC1E* patients.^{23a} Characterization of the proteins governed by

these genes may potentially lead to greater insight into the mechanism of damage to the optic nerve in the absence of high pressures.

In contrast to the above genes, *GLC1C*, located on chromosome 3, appears to produce a glaucoma characterized by high pressure, late onset, and moderate response to glaucoma medications.¹² Although relatively rare, its similarity to POAG suggests that this gene may provide valuable insight into the mechanism of many other types of adult open-angle glaucoma. The glaucoma associated with *GLC1D* also resembles high pressure POAG, and may provide further insights into POAG. *GLC1D* has been mapped to band 23 on the long arm of chromosome 8 (8q23).¹⁵

GLC1F, the fifth locus for POAG, maps to 7q35–36.¹³ Affected individuals have pressures ranging from 22 to 38 mmHg at the time of diagnosis. Pigment dispersion syndrome has been mapped in another family to chromosome 7q35–36, distal of *GLC1F*.²⁴

Each of these gene locations represents only a small fraction of the total open-angle glaucoma population.^{7,25} Their identification indicates the diversity of glaucoma genetics. Given that many other families with glaucoma do not map to these regions, many more glaucoma genes are likely to exist.

ANGLE-CLOSURE GLAUCOMA (GLC2) AND CONGENITAL GLAUCOMA (GLC3)

One angle-closure glaucoma gene and two congenital glaucoma genes have been mapped.^{26–28} Autosomal dominant nanophthalmos (*NNO1*), associated with angle-closure glaucoma due to distortion of the anterior segment, maps to chromosome 11.²⁶ The majority of the congenital glaucoma families map to *GLC3A* on chromosome 2p21.^{27,29,30} Several *GLC3A* families appear to possess mutations in cytochrome P4501B1, resulting in disruption of either the hinge region or the conserved core structures of this enzyme.^{29,31} A second locus for congenital glaucoma, *GLC3B*, which probably affects less than 10% of the cases, has been mapped to chromosome 1p36 (*GLC3B*).²⁸

CURRENTLY IDENTIFIED GLAUCOMA GENES

Discoveries of specific genes associated with certain forms of glaucoma may offer direct insights into glaucoma. Although specific mechanisms are still unknown, these associations do offer opportunities to make general hypotheses. These glaucoma genes include *TIGR* (juvenile and adult-onset glaucoma);⁷ *RIEG*, a homeobox gene (Rieger anomaly);³² *forkhead transcription factor* (congenital glaucoma, Rieger anomaly, Axenfeld anomaly, iris hypoplasia);³³ *LIM-homeodomain gene* (POAG associated with nail-patella syndrome);³⁴ and *CYP1B1* which encodes cytochrome P450 1B1 (congenital glaucoma), also discussed previously.³⁵

As already mentioned, *TIGR* was originally identified based upon its response to glucocorticoids and oxidative stress.⁶ Forkhead transcription factor, *RIEG* and

LIM-homeodomain gene are all transcription factors that are important in development^{32,34,36} and may influence the anterior chamber anomalies associated with these forms of glaucoma. Cytochrome P450 [B] protein is a member of a superfamily of hemoproteins that participate in oxidative metabolism of drugs and also respond to oxidative stress.^{37,38}

Most of the glaucoma genes that have been characterized to date result in developmental glaucomas that are physically distinct from adult-onset POAG. Therefore, a relationship between these genes and POAG seems unlikely. Mutations in some of these genes, however, such as those that cause developmental defects in juvenile glaucoma and nail-patella syndrome, also produce some adult-onset glaucomas. These findings suggest that transcription factors and genes that respond to oxidative stress may be potential candidate genes for POAG. In this manner, understanding the mechanism of how each of these genes results in the above glaucomas may still give fundamental insights into the pathophysiology of POAG.

GENETICS AND DIAGNOSIS OF GLAUCOMA

Localizing glaucoma genes holds great promise for early diagnosis, which can lead to better preservation of vision, even using currently available treatments. This possibility is already available for children of families with juvenile glaucoma. Testing for a *TIGR/MYOC* mutation may reveal those children at high risk of developing severe glaucoma, prompting appropriate IOP monitoring and early, aggressive management. We anticipate a similar possibility for POAG, eventually using noninvasive methods of tissue collection, such as buccal scrapings. As more genes are identified, individuals with and without a family history can ultimately be screened against a battery of glaucoma genes, allowing early diagnosis and prophylactic therapy.

GENETICS AND THERAPY OF GLAUCOMA

The discovery of additional POAG genes will also improve glaucoma therapy. Identifying specific glaucoma genes will lead to more precise glaucoma classification, based on the specific genotype of each family. Since the phenotype, which includes the response to therapy, will be based upon the genotype, we will ultimately be able to select the optimum treatment for a specific individual based on the causal gene, without resorting to "trial and error."

PEARL... Identifying glaucoma genes will eventually improve glaucoma therapy by allowing us to select the optimum therapy based on the patient's genotype, without resorting to "trial and error."

For some glaucomas, optimal treatment may consist of current glaucoma medications and surgery. However, the continued identification of genes with mutations that produce POAG can also lead to treatment with specific, as yet undeveloped, modalities. By defining the protein defect, these discoveries can provide a method for specifically ameliorating glaucoma, first using conventional pharmacological methods and, eventually, newer, still evolving genetic therapies.

GENETICS AND CURRENT GLAUCOMA THERAPY

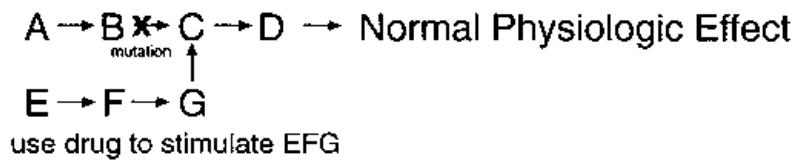
Current treatment, which is now restricted to lowering IOP, may be guided by knowledge of each person's genotype. Patients with a *GLC1A* gene defect may respond best to surgery,^{39,40} whereas medical therapy may be the more appropriate first-round treatment for individuals with mutations in the *GLC1C*, *GLC1D*, or *GLC1F* genes.^{12,13,15} Individuals with mutations of *GLC1B* or *GLC1E*, which are possibly associated with low tension glaucoma, may require treatment of other risk factors, such as optic nerve perfusion.^{14,16}

GENETICS AND GLAUCOMA PHARMACOLOGY

Future traditional pharmacological methods and new genetic approaches to glaucoma therapy will both be most successful when directed toward the ciliary body and trabecular meshwork. Recent pharmacological experience indicates that reducing aqueous humor production can effectively lower IOP, and gene therapy can be used to target aqueous humor reduction without knowing the exact glaucoma gene defect.⁴¹ More exciting is the prospect of improving the aqueous humor outflow through the trabecular meshwork, where the primary defect appears to reside in many POAG patients. Both the trabecular meshwork and the ciliary epithelium are relatively accessible and have been successfully infected by adenovirus vector.^{42,43}

Traditional pharmacological treatments to bypass a gene defect may be developed in the near future (Fig. 2–2). Because defective gene products are often just one step in a complex pathway, triggering the pathway downstream from the defective gene or stimulating a redundant, parallel pathway could alleviate the problem. For example, if *TIGR/MIOC* acts as a stress protein, introducing other stress proteins, such as heat shock protein, either intracamerally or topically, could resolve symptoms. Implementing these types of therapy will require a full understanding of the regulation of these pathways.

These drugs could be produced using recombinant gene technology, through which we can already make insulin, erythropoietin, and human growth hormone, all of which are a form of bypass treatment.⁴⁴ Stromelysin represents a potential example in glaucoma. This enzyme appears to encourage turnover of trabecular meshwork extracellular matrix and thus may enhance the IOP-lowering effect of argon laser trabeculoplasty.⁴⁵ Potentially, injecting a recombinant protein into the anterior chamber



that would induce stromelysin could treat glaucoma in lieu of laser therapy. Identifying the causal genes in specific forms of glaucoma may ultimately allow the design of recombinant proteins to correct these defects.

PEARL... Identifying the causal genes in specific forms of glaucoma may lead to the development of new drugs specifically designed to replace the defective protein.

GENETIC THERAPY OF GLAUCOMA

As described by Weatherall, "Ideally, gene therapy would emulate transplantation surgery and remove a mutant gene and replace it with a normal one."⁴⁶ Genetic therapy for an ocular disease has already been successfully applied to the murine retinal degeneration model of retinitis pigmentosa. In this model, subretinal injections of a recombinant replication-defective adenovirus that contained the murine complementary DNA (cDNA) for the wild-type subunit of

FIGURE 2-2 Bypass treatments. Drug therapy can be used to trigger a parallel pathway to produce a product that will bypass the blocked pathway and produce the normal physiological effect.

the cyclic guanosine monophosphate (cGMP) phosphodiesterase gene delayed photoreceptor cell death by 6 weeks.⁴⁷

This discipline is evolving. Several potential approaches to transferring genetic material to trabecular meshwork cells exist, each with its own advantages and disadvantages. These genetic therapeutic methods include replacing the actual DNA of the gene, modifying mRNA, or replacing a protein. Of these, replacing DNA is most likely to have a permanent effect.

SPECIAL CONSIDERATION

The anterior chamber offers an attractive avenue of access for several potential approaches that may in the future allow us to transfer genetic material to the trabecular meshwork, the probable site of the primary defect in many glaucoma patients.

As summarized in Table 2-2, gene transfer can be accomplished both with and without vectors.⁴⁸ Vectors

TABLE 2-2 POTENTIAL APPROACHES FOR GENETIC GLAUCOMA THERAPY

Treatment	Advantages	Disadvantages
Viral Vector Therapy		
Retrovirus	Integration into genome	Fails to transfect nonduplicating cells May activate oncogenes Limitation in size of gene
Adenovirus	Transfects nonreplicating cells Good efficiency Limitation in size of gene	Immunogenic Transient expression
Herpesvirus	Targets neurons Large genes can be inserted	Limited transfection of blood vessels May be neurotoxic
Nonvector Therapy		
Liposomes	Nonimmunogenic Easy to produce	Low efficiency
Oligonucleotide antisense	Easy to produce	Difficult delivery to specific organ Rapid turnover Possible immune system stimulant Lack of reproducibility
Recombinant proteins	Rapid development time Easy to produce large quantities	Solubility problems for some proteins Rapid turnover
Human artificial chromosomes	Large fragments of DNA can be inserted Long-term expression Nonimmunogenic No risk of mutagenesis from integration into genome	Difficult to prepare large amounts
Ribozymes	Repair directly mutant transcripts Can be used to eliminate mutant transcript Catalytic activity	Reaction has poor specificity Frequency of repair of targeted substrate is unclear

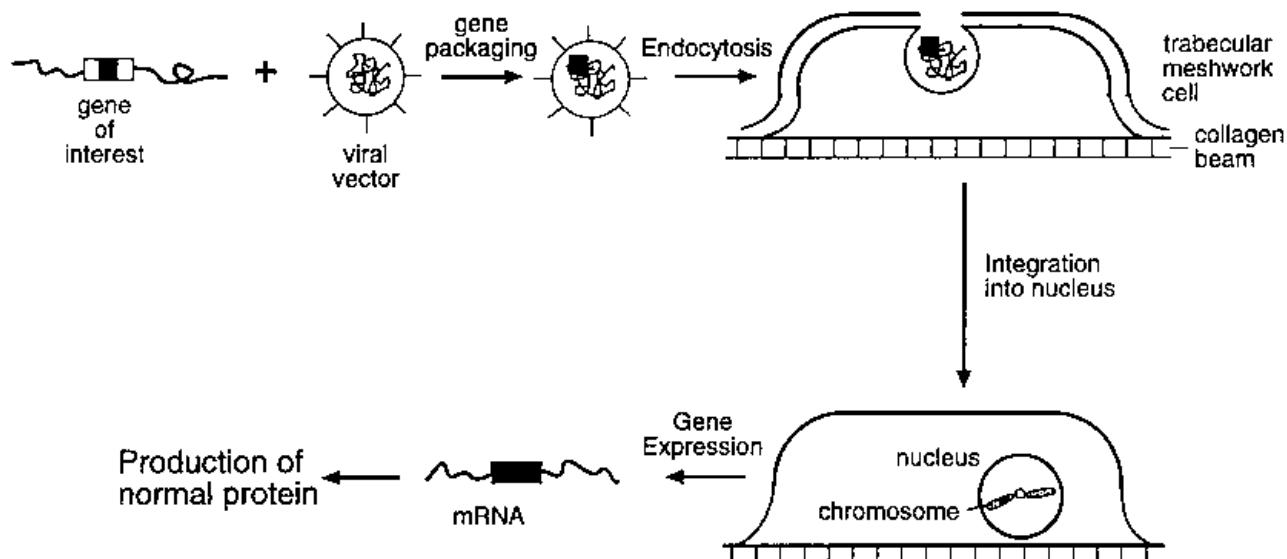


FIGURE 2–3 Gene delivery using a viral vector. The gene of interest is recombined with the vector deoxyribonucleic acid (DNA) (gene packaging). The viral vector fuses with the cell membrane and becomes an endosome within the bilipid layer. The vesicle opens, releasing the vector into the cytoplasm, where the vector is transported to the nucleus. After entering the nucleus, the glaucoma gene is integrated into a chromosome. The gene is expressed and produces a normal protein. (Reproduced with permission from Wirtz MK, Acott TA, Samples JR, Morrison JC. Prospects for genetic intervention in adult-onset glaucoma. *Drugs Aging* 1998;13:333–340.)

include the retrovirus, herpesvirus, and adenovirus (Fig. 2–3). Because it requires actively replicating cells, and trabecular cell division is slow,^{49,50} the retrovirus may be least efficient for treating glaucoma. Herpesvirus, which can transfect neurons, may be useful for directly treating the retina and optic nerve head.⁴⁸ Although limited both by transient expression and by the size of genes it can transfer,⁴⁸ the adenovirus shows the most promise for delivery to the trabecular meshwork. It does not require cell mitosis and can deliver reporter genes to the trabecular meshwork.^{42,43} In fact, the high uptake of the virus by trabecular meshwork cells, possibly aided by their high phagocytic capacity, indicates that this tissue may be one of the easiest targets for this form of gene delivery.⁴² Although viral vector therapy has much potential, it has not yet been done in humans, and viruses may have dangerous side effects, such as insertional mutagenesis.⁴⁶

Nonvector therapies have more immediate potential and greater versatility and may be more readily accepted. They can replace defective genes, inhibit transcription, correct mutant RNA, and directly replace needed protein (Figs. 2–4A,B; 2–5A,B). Cationic liposomes are an attractive alternative to viral transfer because they have lower immunogenicity and no DNA size constraints. However, liposome transfection efficiency of nondividing cells is very low.⁵¹ Targeting liposomes with directive antibodies or binding proteins specific for the surface of trabecular cells may overcome this disadvantage.

Human artificial chromosomes (HACs) present another intriguing potential gene therapy (Fig. 2–4B) because cell replication is not required. Given that both the gene and its regulation sequence are inserted, the gene is turned off and on appropriately.^{52,53} Once in the nucleus, the artificial chromosome is replicated along with the host chromosomes, providing a permanent, one-time therapy.

Ribozymes are RNA molecules with enzymatic activity (Fig. 2–5A). They bind to a specific RNA sequence and cleave it at a unique site,⁵⁴ thereby replacing the mutant with normal mRNA and restoring the wild-type gene production.⁵⁵ Ribozymes and antisense oligonucleotides are both potential treatments for *GLC1A* through *GLC1F* because all demonstrate autosomal dominant inheritance.

Antisense therapy (Fig. 2–5B) involves using either vectors or liposomes to add a complementary sequence of RNA or DNA (antisense) to the cytoplasm. This sequence binds to the mutant mRNA, targets it for rapid destruction by nucleases, and blocks production of the abnormal protein.^{54,56} Antisense oligonucleotides may be effective in dominant negative diseases, such as osteogenesis imperfecta, where the individual expresses both the normal and the mutant copy of the gene. If some forms of POAG prove to result from similar dominant negative interactions, antisense therapy is probably the simplest and most effective method for inhibiting synthesis of the resulting mutant peptide. Ultimately, the effectiveness of antisense therapy depends upon the molecular biology of the defective peptide.

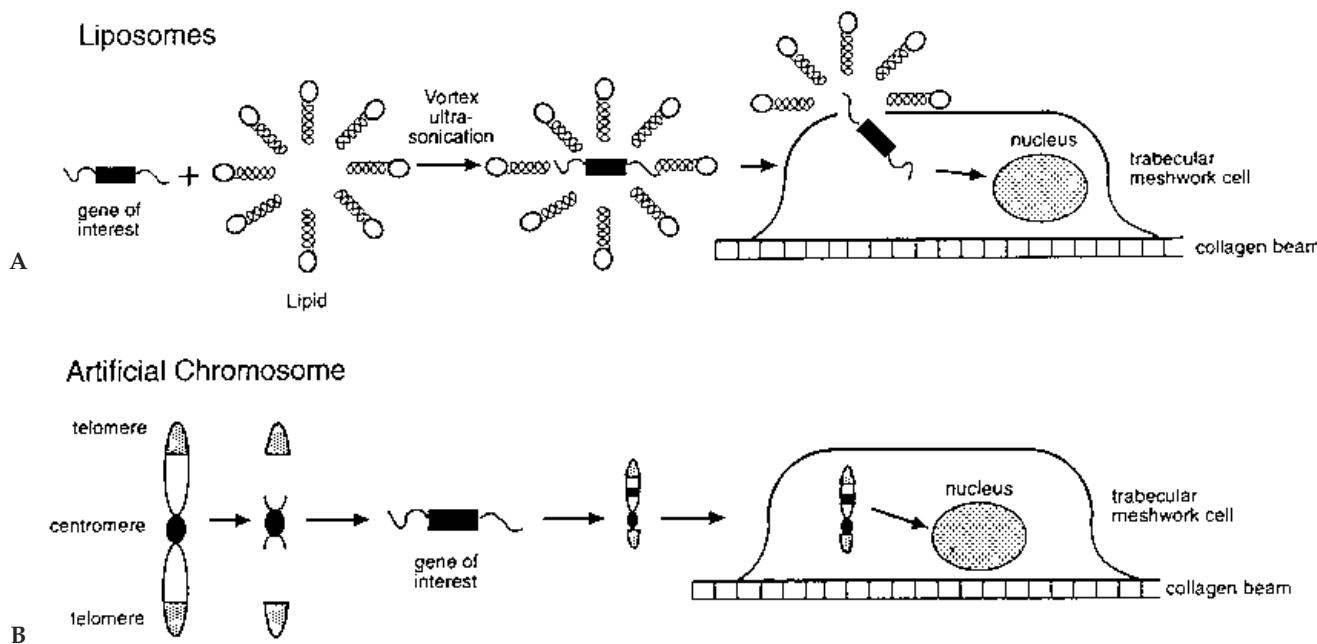


FIGURE 2-4 Nonviral therapy targeted to chromosomal integration. (A) Liposomes. The glaucoma gene is mixed with cationic liposomes, resulting in the formation of a deoxyribonucleic acid (DNA)/liposome complex. This complex allows transfer of the DNA through the also negatively charged cell membrane. (B) Artificial chromosomes are created by combining a centromere, two telomeres, and the gene of interest. This chromosome will then be taken up by the nucleus, and the glaucoma gene can be normally transcribed. (Reproduced with permission from Wirtz MK, Acott TA, Samples JR, Morrison JC. Prospects for genetic intervention in adult-onset glaucoma. *Drugs Aging* 1998;13:333–340.)

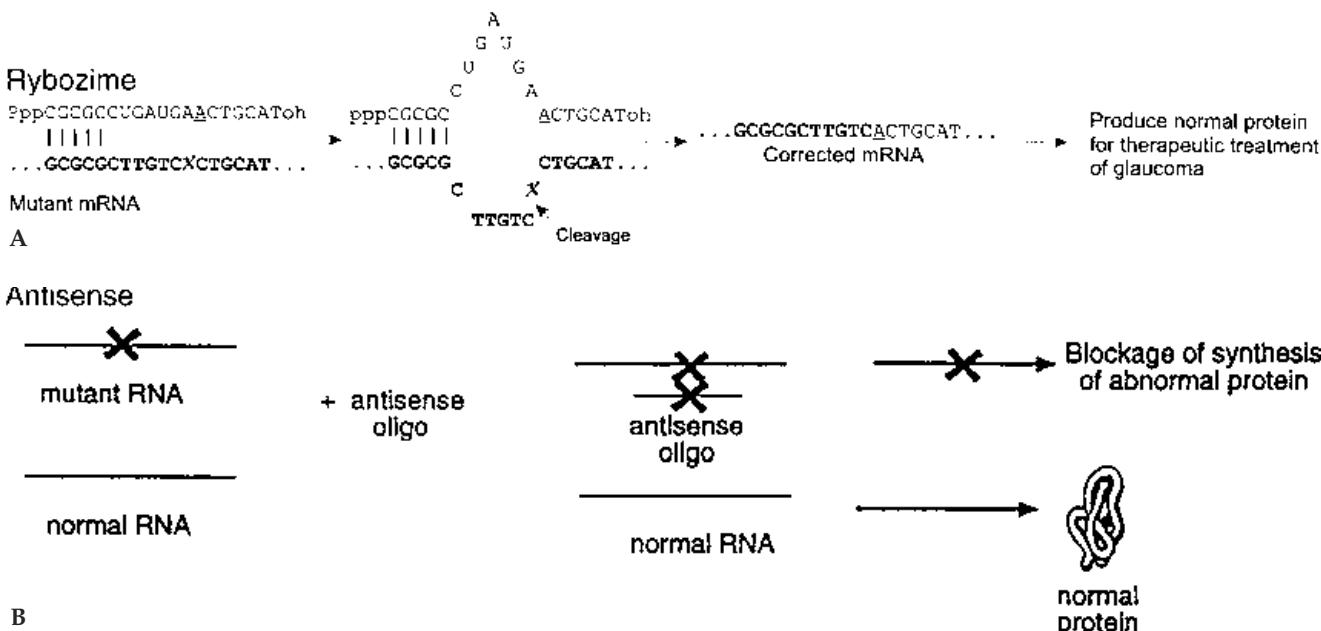


FIGURE 2-5 (A) Nonviral therapy targeted to the cytoplasm. Ribozymes can be designed to react with a target ribonucleic acid (RNA) by varying their nucleotide composition at the 5' end to bind to any specified region of the mutant messenger RNA (mRNA). The sequence "CUGAUGA" in the ribozyme produces cleavage of the substrate RNA at the mutant nucleotide (χ) and ligates the resulting new 3' end onto its own 3' region, which contains the correct nucleotide (A). By designing the ribozyme to bind upstream of the mutation, the RNA can be cleaved and the mutation replaced with the normal sequence. (B) Antisense oligonucleotides will bind to the mutant RNA and block the synthesis of the mutant glaucoma gene, allowing synthesis of normal protein. (Reproduced with permission from Wirtz MK, Acott TA, Samples JR, Morrison JC. Prospects for genetic intervention in adult-onset glaucoma. *Drugs Aging* 1998;13:333–340.)

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SECTION II

DETERMINANTS OF INTRAOCULAR PRESSURE

ANATOMY AND PHYSIOLOGY OF AQUEOUS HUMOR FORMATION

John C. Morrison, M.D., Thomas F. Freddo, O.D., and Carol B. Toris, Ph.D.

Glaucoma management relies heavily on measuring and controlling intraocular pressure (IOP), and on a thorough understanding of the anatomy and physiology that underlie formation and elimination of aqueous humor. Aqueous humor maintains the optical properties of the eye by stabilizing the ocular structure and nourishing the avascular lens and cornea. Aqueous humor formation begins with ultrafiltration of plasma from the ciliary process capillaries followed by active secretion into the posterior chamber by the ciliary epithelium. This is best understood by considering the overall ocular blood supply, followed by the specifics of the anterior uveal microcirculation and, finally, the histology and ultrastructure of the ciliary processes. Aqueous humor secretion, which makes the greatest contribution to aqueous formation, relies on the structural integrity of the blood–aqueous barrier and active transport of solutes, particularly Na^+ , to create a standing osmotic gradient between nonpigmented epithelial cells. This encourages the flow of water and other substances into the posterior chamber. The natural regulation of aqueous formation follows a circadian pattern, governed in part by circulating catecholamines.

ANATOMY OF AQUEOUS HUMOR FORMATION

GENERAL ANATOMY OF THE ANTERIOR SEGMENT

The aqueous humor-containing anterior segment is separated by the lens–iris diaphragm into anterior and posterior chambers (Fig. 3–1). The cornea forms the roof of the anterior chamber, and the iris its floor. The anterior chamber angle, consisting specifically of the trabecular meshwork and the face of the ciliary muscle, forms the lateral boundary of the anterior chamber. The peripheral boundary of the cornea, Schwalbe's line, marks the end of

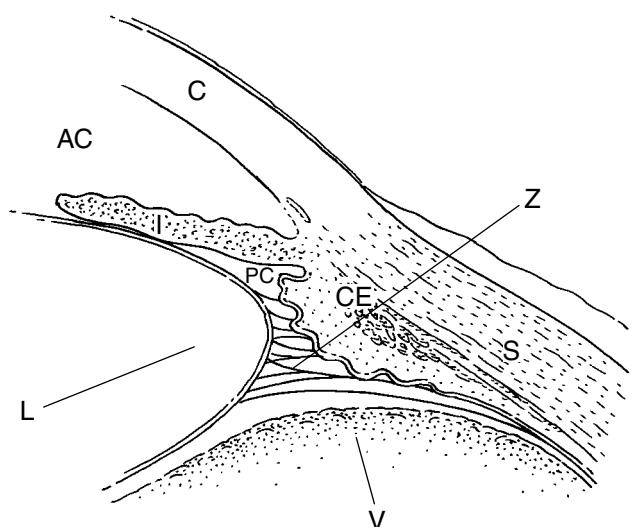


FIGURE 3–1 Aqueous humor-containing compartments of the eye. L, lens; Z, zonules; V, anterior vitreous face; AC, anterior chamber; PC, posterior chamber; C, cornea; S, sclera, I, iris; CB, ciliary body.

normal corneal endothelium, and its basement membrane, Descemet's membrane. Here the anterior chamber angle begins, with the initial beams of the trabecular meshwork.

The posterior chamber is bordered in part by the inner surface of the ciliary body, which is grossly subdivided into the pars plicata and pars plana. Whereas the former is corrugated to maximize surface area, consistent with its secretory role in aqueous humor formation, the latter possesses a smooth surface, beneath which is a thin layer of stroma and longitudinal ciliary muscle fibers that end at the ora serrata, the limit of the peripheral retina. The floor of the posterior chamber consists of the anterior face of the vitreous body, which is firmly attached to the posterior pars plana and the ora serrata. Most of the

aqueous humor formed by the pars plicata flows anteriorly around the zonules and lens, and through the pupil before exiting the eye at the anterior chamber angle.

OCULAR BLOOD SUPPLY

The blood supply to the eye is derived entirely from the ophthalmic artery, which arises from the internal carotid artery (Fig. 3–2A). The ophthalmic artery enters the orbit through the optic canal, lying within the inferior adventitial sheath of the optic nerve. Once within the orbit, the ophthalmic artery provides several major ocular branches, the exact order of which can be quite variable. In general, these include the central retinal artery, two posterior ciliary arteries, and medial and lateral muscular arteries.

Whereas the central retinal artery enters the ventral aspect of the optic nerve 5 to 15 mm behind the eye, the posterior ciliary arteries travel forward on either side of

the optic nerve. They give rise to 15 to 20 short posterior ciliary arteries that enter the sclera in a ring around the nerve. These arteries, along with the central retinal artery, supply the retina, choroid, optic nerve, and optic nerve head (see Chapter 8).

In addition to short posterior ciliary arteries, the posterior ciliary arteries also give rise to medial and lateral long posterior ciliary arteries. These enter the sclera nasally and temporally to the optic nerve and travel along the horizontal equator within the suprachoroidal space toward the anterior segment. Here they join perforating branches of the anterior ciliary arteries to supply the iris and ciliary body.

Additional ocular vessels arising from the ophthalmic artery within the orbit include the medial and lateral muscular branches. The medial branch supplies arteries to the medial, inferior, and lateral rectus muscles, whereas the lateral branch supplies the superior rectus muscle. All of these arteries travel anteriorly within the muscle, and all but that

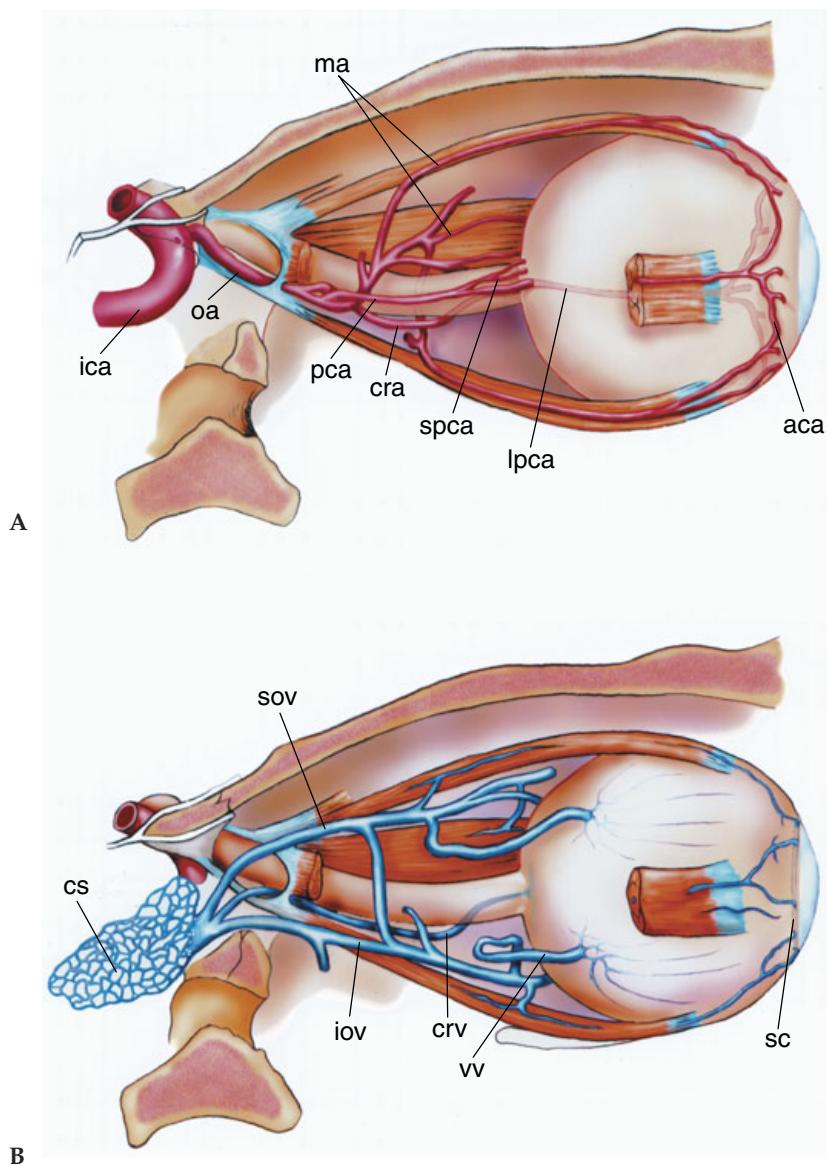


FIGURE 3-2 (A) Ocular blood supply. ica, internal carotid artery; oa, ophthalmic artery; pca, posterior ciliary artery; cra, central retinal artery; ma, muscular arteries; spca, short posterior ciliary arteries; lpca, long posterior ciliary artery; aca, anterior ciliary arteries. (B) Venous drainage from the eye. cs, cavernous sinus; crv, central retinal vein; vv, vortex vein; sc, Schlemm's canal; sov, superior ophthalmic vein; iov, inferior ophthalmic vein.

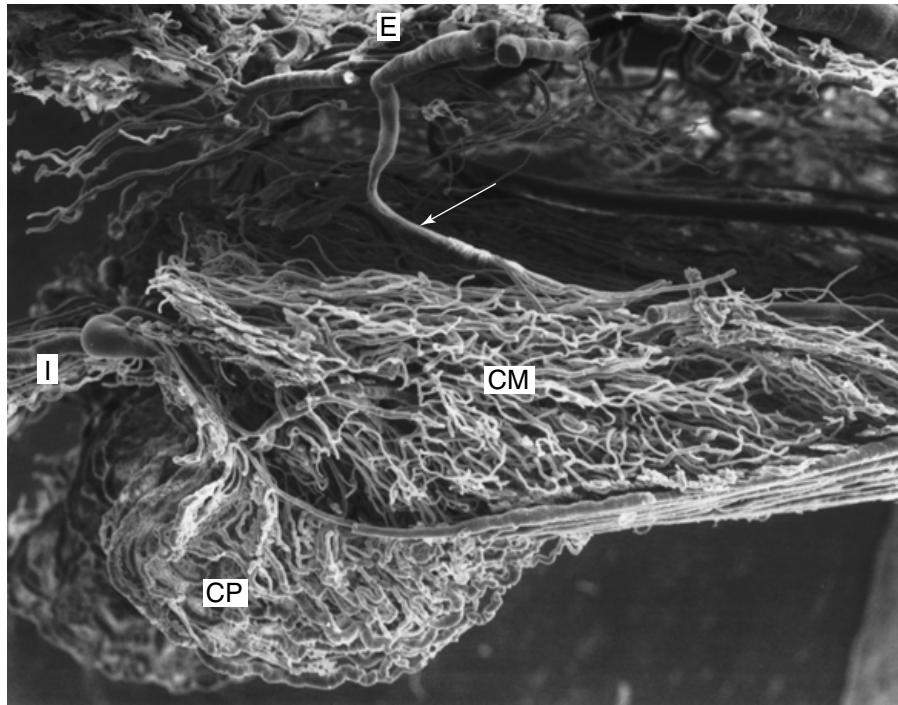


FIGURE 3-3 Profile view of a vascular luminal casting of the primate ciliary body, following chemical removal of tissue. Episcleral vasculature (E) is connected to the ciliary muscle capillary bed (CM) by a perforating arteriole (arrow) that spans the limbus. I, iris; CP, ciliary process. (X95) (Reprinted with permission from Ritch R, Shields MB, Krupin T, eds. *The Glaucomas*. St. Louis, Mo: Mosby; 1996:252–253.)

in the lateral rectus muscle split into two arteries. At the insertion of the muscles into the sclera, these arterioles branch into the anterior ciliary arteries and form an incomplete collateral vascular network within the episclera. Branches from these vessels then pierce the limbal sclera as perforating arterioles to enter the ciliary muscle capillary bed (Fig. 3-3). Within this bed, these vessels arborize extensively, forming an anastomosis with each other and with branches from the long posterior ciliary arteries. Thus the anterior and long posterior ciliary vessels combine to supply the iris, ciliary processes, and ciliary muscle.

Figure 3-2B illustrates the major patterns of venous drainage from the eye. Some blood from the anterior uvea flows into episcleral veins, which also receive aqueous humor from the trabecular meshwork and Schlemm's canal. However, most of the blood from the iris and ciliary body drains into the vortex veins. Episcleral veins drain primarily into the veins of the extraocular muscles and then into the superior and inferior ophthalmic veins, along with blood from the vortex veins.

Posteriorly, the central retinal vein, which receives the bulk of venous drainage from the optic nerve head, exits the eye in a common adventitial sheath with the central retinal artery. Traveling beneath the optic nerve, the central retinal vein leaves the orbit through the optic canal and joins the superior and inferior ophthalmic veins to empty into the cavernous sinus.

BLOOD SUPPLY TO THE ANTERIOR UVEA

The anterior uvea comprises the iris and the ciliary body with its ciliary processes. All of these structures receive blood from the extensive anastomoses formed within the

ciliary muscle by the long posterior ciliary arteries and anterior ciliary arteries.¹ Collateral circulation exists in the episclera, between branches of the anterior ciliary arteries, and within the ciliary muscle. The latter, more extensive anastomoses are formed between perforating branches of the anterior ciliary arteries and the two long posterior ciliary arteries. Some branches from this “intramuscular circle” supply the capillary bed of the ciliary muscle. Other branches travel anteriorly to the iris root, where they bend or branch at right angles to form the “major arterial circle” of the iris. Although continuous in many mammals, this “circle” in primates is generally discontinuous and exists primarily at the root of the iris, rather than actually in the iris.

SPECIAL CONSIDERATION

Collateral blood supply to the anterior uvea consists of three anastomotic “circles”: (1) the episcleral circle, formed by branches of anterior ciliary arteries; (2) the intramuscular circle, consisting of branches from the long posterior and perforating anterior ciliary arteries; and (3) the discontinuous “major arterial circle” at the root of the iris, formed by anterior extensions of the intramuscular circle.

Branches from the major arterial circle supply arterioles to the iris as well as to the ciliary processes.² Ciliary process arterioles arise from the major arterial circle of the

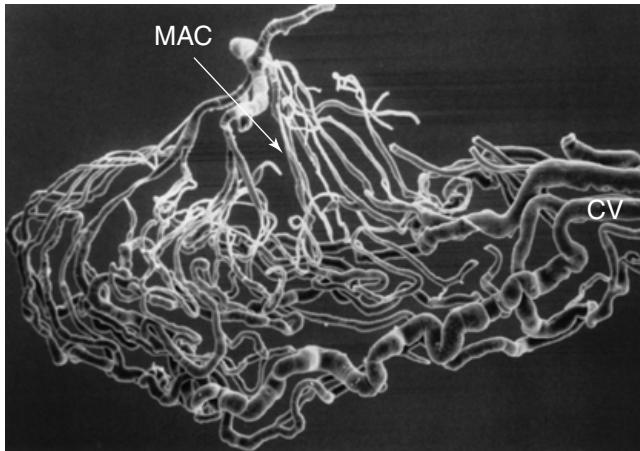


FIGURE 3-4 Ciliary process casting. Major arterial circle (MAC) supplies anterior (arrow) and posterior (arrowhead) arterioles to the process. Anterior arterioles supply capillaries to the anterior and marginal regions of the process. Capillaries drain posteriorly, into the choroidal veins (CV) (X145).

iris in a fan shape. On entering the ciliary processes, these vessels expand to form dilated, irregular capillaries (Fig. 3-4). Interprocess vascular connections have been described between major ciliary processes, as well as to the intervening minor processes.³ The anterior arterioles supply the anterior regions and margins of the processes, and these capillaries travel in a posterior direction to empty into iris veins. These veins, which also receive blood from the ciliary muscle, continue posteriorly to join the vortex veins.

ANATOMY AND HISTOLOGY OF THE CILIARY BODY

The ciliary body, along with the iris, forms the anterior uvea. The ciliary muscle, which forms the outer portion of the ciliary body, is a triangular tissue consisting of three groups of muscle fibers, with its apex pointing posteriorly, ending at the ora serrata. Outermost, longitudinal fibers insert as tendinous bands into the scleral spur, with some extending in front of the spur, into the trabecular meshwork. The middle radial and inner circular fibers form the base of this triangle and can be seen gonioscopically as the ciliary body band.

Internal to the ciliary muscle, approximately 70 radial ciliary processes and intervening minor processes extend into the posterior chamber, forming the pars plicata (Fig. 3-5). These processes arise just posterior to the iris root, forming the ciliary sulcus. Major processes are approximately 2 mm long and 1 mm high and have irregular, convoluted surfaces. The more posterior pars plana, which only overlies the ciliary muscle, extends from the ciliary processes to the ora serrata. Lens zonules arise from between the nonpigmented epithelial cells and are channeled in between the ciliary processes to insert into the anterior and posterior lens capsule.

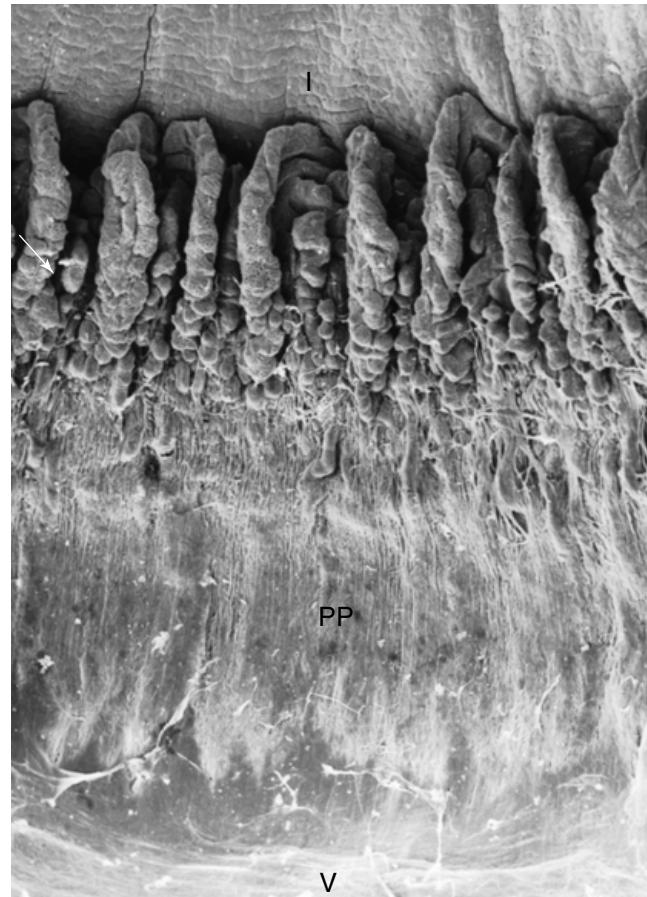


FIGURE 3-5 Scanning electron micrograph of the posterior chamber with lens and zonules removed demonstrates posterior surface of the iris (I), major and minor ciliary processes (pars plicata), and pars plana (PP). Ora serrata and vitreous base (V) are located at the bottom of photograph (X42). (Reprinted with permission from Ritch R, Shields MB, Krupin T, eds. *The Glaucomas*. St. Louis, Mo: Mosby; 1996:252–253.)

Ciliary processes are the site of aqueous humor formation. Histologically, each process consists of a fibrovascular core and a double-layered epithelium that is continuous posteriorly with the pars plana (Fig. 3-6). This arrangement serves the process of aqueous humor formation, which consists of ultrafiltration of plasma through the capillary endothelium, followed by active secretion of aqueous by the ciliary epithelium into the posterior chamber.

ULTRASTRUCTURE OF THE CILIARY PROCESS MICROVASCULATURE

Capillaries of the ciliary muscle have a continuous endothelial lining that is impermeable to injected tracer substances. In contrast, the capillaries of the ciliary processes have fenestrations, consisting of circular “pores” where the cell membranes are fused.⁴ These fenestrations, which line the entire circumference of these

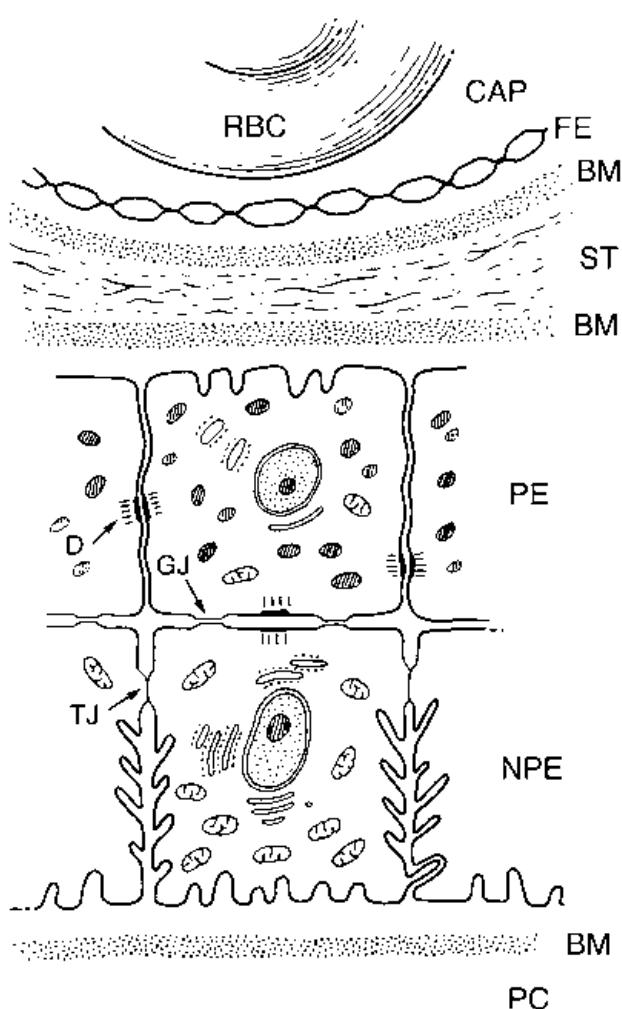


FIGURE 3-6 Schematic illustration of the ciliary process histology, demonstrating capillary (CAP) with fenestrated endothelium (FE), ciliary process stroma (ST), and pigmented (PE) and nonpigmented (NPE) epithelium. TJ, tight junctions; GJ, gap junctions; D, desmosomes; BM, basement membrane; PC, posterior chamber.

capillaries, allow for the passage of macromolecules, including tracer substances like horseradish peroxidase, into the ciliary process stroma⁵ (Fig. 3-7). This forms the ultrastructural basis for ultrafiltration.

PEARL... Fenestrated capillaries, a loose connective tissue stroma, and a metabolically active, double-layered epithelium form the histologic basis for aqueous humor formation by ciliary processes.

ULTRASTRUCTURE OF THE CILIARY PROCESS EPITHELIUM

The ciliary process epithelium provides the site of aqueous humor secretion and the anatomical basis of the blood-aqueous barrier. This epithelium consists of two simple epithelial layers joined apex to apex, with the basal lamina of the pigmented layer adjacent to the stroma and that of the nonpigmented epithelium lining the posterior chamber. This arrangement occurs because the optic vesicle invaginates to form the optic cup during development. The nonpigmented ciliary epithelium is continuous anteriorly with the pigment epithelium of the iris and posteriorly with the neurosensory retina. The pigmented epithelium corresponds anteriorly to the anterior myoepithelium of the iris and posteriorly to the retinal pigment epithelium.

Pigmented epithelial cells contain numerous melanosomes and moderate amounts of mitochondria, rough endoplasmic reticulum, and Golgi (Figs. 3-6 and 3-8). In contrast, nonpigmented epithelial cells have a highly redundant basal surface lying on a thin basal lamina with lateral interdigitations. These cells lack melanin but have numerous mitochondria and more extensive rough endoplasmic reticulum, suggesting greater metabolic activity. These features are more easily seen along the margins of the anterior parts of the ciliary processes,

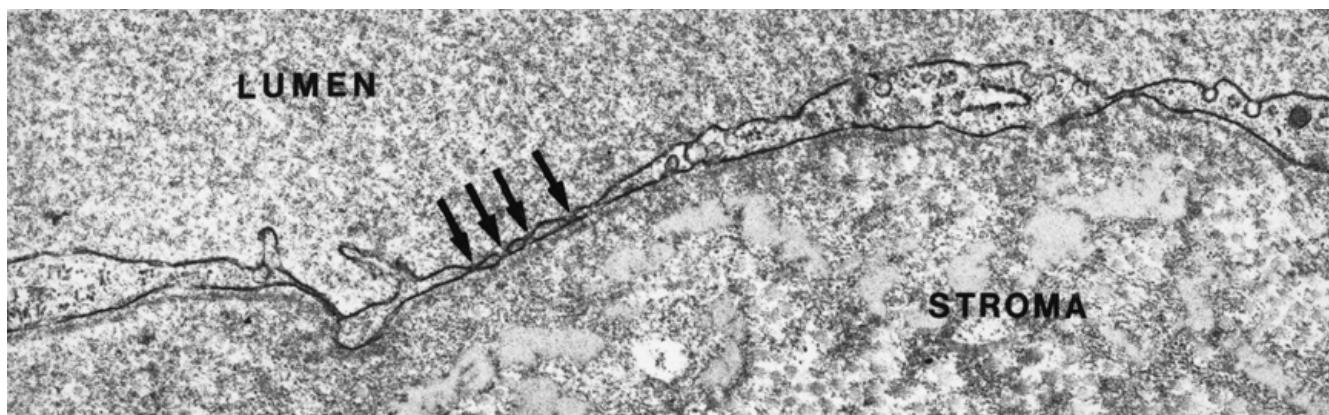


FIGURE 3-7 Ciliary process capillary wall following injection of horseradish peroxidase. Electron dense tracer is seen in both the capillary lumen and the process stroma. Arrows indicate endothelial fenestrations X26,000. (Reprinted with permission from Ritch R, Shields MB, Krupin T, eds. *The Glaucomas*. St. Louis, Mo: Mosby; 1996:252–253.)

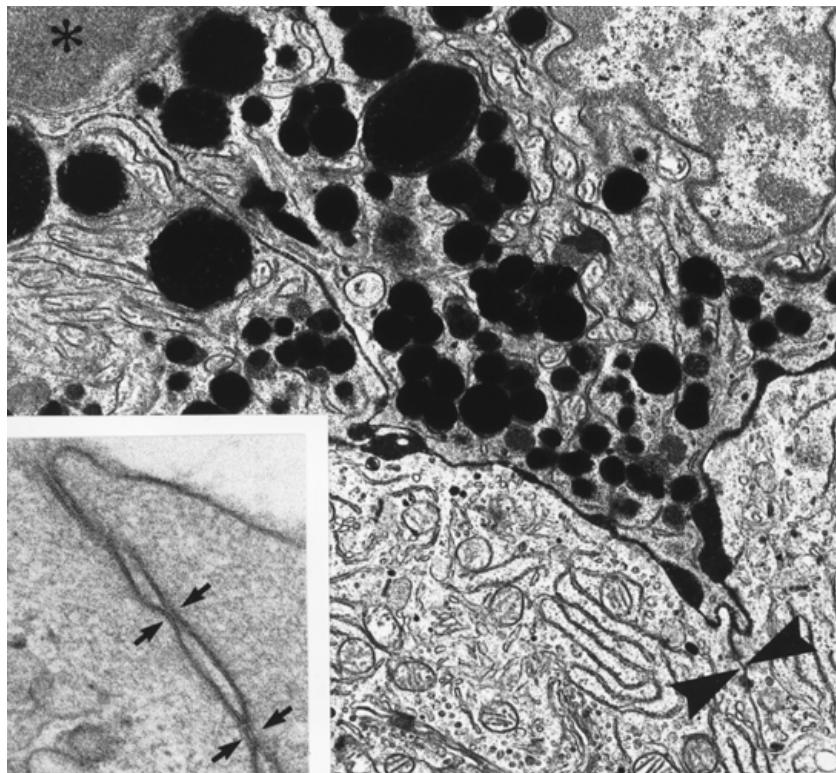


FIGURE 3-8 Transmission electron micrograph of ciliary process epithelium following injection of horseradish peroxidase. Pigmented epithelium, at top, has numerous black melanosomes, whereas nonpigmented epithelium has increased mitochondria and endoplasmic reticulum. Tracer is evident in capillary lumen (*) and is seen between pigmented and nonpigmented epithelial cells. A tight junction (arrowheads) blocks diffusion into intercellular cleft between nonpigmented cells (X19,000). Inset: High-power view shows fusion between nonpigmented epithelial cell membranes that constitutes the tight junction (X131,000). (Reprinted with permission from Ritch R, Shields MB, Krupin T, eds. *The Glaucomas*. St. Louis, Mo: Mosby; 1996:252–253.)

regions thought more likely to be involved in producing aqueous humor.^{6,7,8}

Specialized intercellular junctions are seen throughout both layers of the ciliary process epithelium.^{9,10} These include desmosomes and gap junctions within and between both layers. The former are responsible for maintaining attachments between the cytoskeleton of adjacent cells. The latter, consisting of aggregates of intramembranous proteins, called connexons, that form a tube between cells, allow ions and small molecules such as amino acids, sugars, and nucleotides to move between them. These allow the two layers of epithelial cells to operate as a functional syncytium for the production of aqueous humor. Hypotony in experimental uveitis has been correlated with marked reduction of these gap junctions.¹¹

Another type of cell junction, zonula occludens or tight junction, exists only between nonpigmented epithelial cells near their apices, forming the blood–aqueous barrier at the apex of intercellular clefts.^{9,12,13} These junctions consist of a system of continuous anastomosing linear strands of direct contact between cell membranes (Fig. 3–9). They form a band around the epithelial cells and prevent passage of macromolecules from the stroma into the posterior chamber. These tight junctions, the permeability of which is inversely related to their complexity, produce an apparently selective barrier, restricting movement of macromolecules into the posterior chamber. This allows the diffusion of water and small molecules into the posterior chamber while helping maintain the osmotic gradient across the ciliary epithelium that is necessary for active transport to occur.¹⁴

PEARL... The zonula occludens, a system of anastomosing linear strands of direct contact between the apical cell membranes of adjacent, nonpigmented epithelial cells, forms the blood–aqueous barrier.

PHYSIOLOGY OF AQUEOUS HUMOR FORMATION

AQUEOUS HUMOR FUNCTION

Aqueous humor serves several purposes. It helps maintain eye pressure at a level that will preserve the normal ocular structure and function. In addition, it supports the metabolic functions of the avascular structures of the eye, particularly the lens, cornea, and trabecular meshwork. In doing so, aqueous humor supplies glucose, oxygen, and amino acids and removes waste products, such as lactic acid and carbon dioxide.^{15,16}

AQUEOUS HUMOR COMPOSITION

Numerous studies have been performed on the composition of aqueous humor. Its components and their concentrations are listed in detail elsewhere.^{17,18} In general, this composition is initially determined by the properties of the aqueous as it is formed by the ciliary processes. Later changes occur from contact with the vitreous, lens, iris, and cornea as the aqueous moves from the posterior into the anterior chamber.

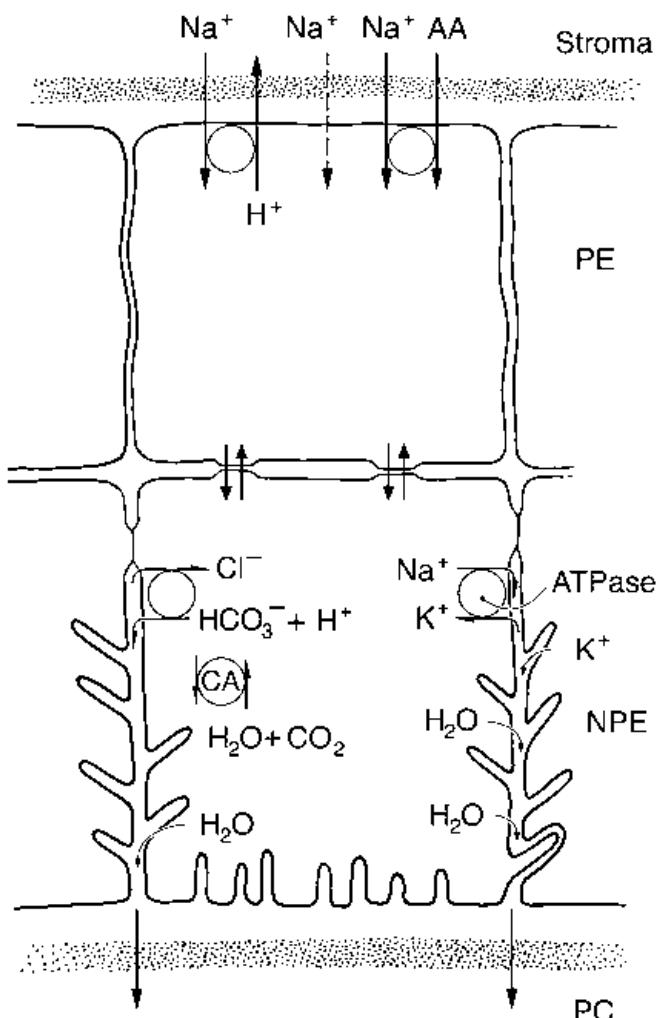


FIGURE 3-9 Schematic diagram illustrating the potential mechanisms of aqueous humor secretion. Active exchangers and cotransporters as well as ion channels move small molecules from the ciliary process stroma into the pigmented epithelium. Gap junctions allow movement between the pigmented and nonpigmented epithelium. Active transport of Na^+ by adenosinetriphosphatase into the intercellular clefts just below tight junctions is the predominant factor in establishing an osmotic gradient, encouraging passive movement of water and ions into the clefts and, ultimately, the posterior chamber. PE, pigmented epithelium; NPE, nonpigmented epithelium; AA, amino acids; PC, posterior chamber; CA, carbonic anhydrase; ATPase, sodium: potassium-dependent adenosinetriphosphatase.

Several differences between aqueous humor and plasma strongly suggest that aqueous is not a simple ultrafiltrate. This implies the existence of a specific active secretory mechanism, to be discussed below. The main difference is the protein content, due most likely to the function of the tight junctions of the normal blood-aqueous barrier.¹⁹

SPECIAL CONSIDERATION

Several differences between aqueous humor and plasma, including low aqueous humor protein and high ascorbate levels, strongly suggest that aqueous is not a simple ultrafiltrate of plasma.

Aqueous humor contains less than 1% of the protein found in plasma, with a ratio of 0.024:7 g/dL. The plasma-derived proteins present in aqueous generally reflect their relative concentrations in plasma,^{20,21} but with lower concentrations of those proteins with higher molecular weights. Exceptions include transferrin, an iron-scavenging protein that is found in higher concentration in aqueous than in plasma.²² Still other polypeptides and proteins are locally produced within the tissues of the eye and serve an array of recently identified regulatory functions. Many of these are growth factors. The most thoroughly investigated of these is transforming growth factor-beta (TGF- β), which is known to play important roles in the unique immunoregulatory processes of anterior chamber acquired immune deviation (ACAIID).²³ It also has been shown that TGF- β may be present in higher concentrations in the aqueous humor of patients with adult primary open-angle glaucoma (POAG) than in age-matched healthy subjects.²⁴ The significance of this finding is unknown. Amino acids are present in variable amounts. Overall, disruption of the blood-aqueous barrier increases protein concentration²⁵ and produces a relative increase in proteins specifically involved in coagulation and fibrinolysis.²⁶

Recently, the novel TIGR, or myocilin, protein has been immunohistochemically localized to the inner uveal and anterior portion of the trabecular meshwork in normal human eyes. This protein, which can be induced by exposure of trabecular cell cultures to glucocorticoids (see Chapter 18),^{27,28} is also present in human aqueous humor.²⁹

Evidence suggests that plasma-derived protein in the aqueous humor of the anterior chamber is supplemented just prior to its entry into the outflow pathway. Magnetic resonance imaging with contrast materials has demonstrated that plasma-derived proteins move from a depot in the ciliary body stroma to the root of the iris, bypassing the posterior chamber and entering the anterior chamber near the trabecular meshwork.³⁰⁻³² A potential function of these additional proteins is that some, particularly those of low molecular weight, may contribute to normal aqueous outflow resistance as they interact with the extracellular matrix of trabecular meshwork.³³⁻³⁵

Normal aqueous humor also differs from plasma by a nearly 30-fold increase in the level of ascorbate, due to active secretion.³⁶ Diffusional exchange across the iris probably lowers this concentration in the anterior chamber compared with the posterior chamber. Potential functions

of aqueous humor ascorbate include antioxidant protection as well as protection of the lens from ultraviolet radiation.³⁷ In the human, aqueous humor tends to be slightly acidic with decreased bicarbonate, compared with plasma.³⁸

AQUEOUS HUMOR FORMATION

Passage of aqueous humor into the posterior chamber is generally felt to occur through a combination of three processes: ultrafiltration, active secretion, and diffusion. Ultrafiltration describes the movement of water and water-soluble substances across a cell membrane. This is governed by the relative osmotic and hydrostatic pressure gradients that exist between the capillaries and stroma within the ciliary processes. Secretion is a metabolically active process that moves solutes across the cell membrane. In the eye, this process creates an osmotic gradient that drives the movement of water and other solutes into the posterior chamber. Under normal physiological conditions, active secretion may account for 80 to 90% of total aqueous humor formation.³⁹ Diffusion is the passive movement of substances across a cell membrane down a concentration gradient.

It is unlikely that ultrafiltration across the ciliary epithelium contributes to a large proportion of aqueous humor formation. This is supported by the marked differences in composition between aqueous and plasma already mentioned, and several additional observations. These include the fact that variations in systemic blood pressure do not significantly influence aqueous formation,⁴⁰ and reports that metabolic inhibitors of active secretion can markedly diminish aqueous formation.⁴¹ Finally, physiological measurements of osmotic and hydrostatic forces across the ciliary process epithelium appear to favor reabsorption of aqueous humor, rather than movement into the posterior chamber.⁴⁰

In spite of these considerations, ultrafiltration represents an important first step in aqueous humor production. This is the most likely mechanism by which plasma constituents gain entry into the ciliary process stroma, creating a pool upon which the active secretory processes within the epithelium can act to move solutes into the posterior chamber. The capillaries of the ciliary processes are unusually permeable and the ultrafiltrate is rich in proteins, about 60% of that present in plasma.⁴²

Following ultrafiltration, the next step in aqueous formation is active secretion of ions by the nonpigmented layer of the ciliary epithelium. The tight junctions between the nonpigmented ciliary epithelial cells ensure that the accumulation of ions in the intercellular cleft creates a strong osmotic gradient, along which water will flow into the posterior chamber⁴³ (see Fig. 3–9). This is the standing-gradient osmotic flow mechanism coupling water and solute transport.⁴⁴

There are likely several secretory processes responsible for active solute transport across the ciliary epithelium (see Fig. 3–9). Sodium transport appears to be the principal

mechanism for water movement. Sodium is transported into the clefts by a sodium-potassium-activated adenosinetriphosphatase (ATPase). High concentrations of this enzyme exist in the lateral interdigitations of the nonpigmented ciliary epithelium, a likely site of aqueous humor secretion.^{45,46} Inhibition of this enzyme with ouabain will substantially diminish the production of aqueous humor.⁴¹

The electrochemical imbalance created by the transport of sodium is corrected by negatively charged ions that follow the sodium. One of these ions is bicarbonate produced by the enzyme carbonic anhydrase, which catalyzes the interconversion of H_2O and CO_2 to HCO_3^- and H^+ . This enzyme has been localized in the nonpigmented epithelium.^{45,47} Carbonic anhydrase inhibitors can substantially reduce aqueous production (see Chapter 38). In addition to providing HCO_3^- for movement with Na^+ into the intercellular clefts, carbonic anhydrase may also help maintain the proper pH for the function of Na^+/K^+ -dependent ATPase.^{48,49} The H^+ that results from this reaction can also be exchanged with Na^+ , providing adequate intracellular sodium for transport.

Active transport of other ions, including Cl^- and K^+ , also may contribute to the secretory process.^{50,51} Gap junctions between pigmented and nonpigmented epithelial cells allow the movement of solutes between these two layers, providing access for passive transport into the posterior chamber along the osmotic gradient, via specific ion channels.⁵² The presence of the tight junctions connecting nonpigmented epithelial cells at the apex of intercellular clefts, which prevent the movement of most solutes, is essential for the formation and maintenance of the osmotic gradient.

Substances, such as oxygen and glucose, that are necessary for the health of the lens and cornea do not enter the aqueous as part of active secretion. These pass the blood-aqueous barrier by simple or facilitated diffusion. Their consumption from the aqueous by the lens and cornea establishes a concentration gradient that is the driving force for the continued diffusion of these substances into the posterior chamber. Therefore, the diffusion rate of these substances does not depend upon the aqueous formation rate. However, a constant flow of aqueous is necessary to flush out the waste products. Marked reduction of aqueous formation rate may increase the concentrations of potentially harmful substances in the anterior chamber.

REGULATION OF AQUEOUS HUMOR FORMATION

In practice, aqueous humor formation is considered equivalent to the clearance rate of fluorescein from the anterior chamber (see Chapter 7). This clearance rate is a function of the rate of flow of aqueous humor from the posterior chamber into the anterior chamber. The measurement does not account for any aqueous that leaves the posterior chamber by other routes such as through the vitreous cavity. Aqueous flow, therefore, is somewhat less than

aqueous formation. In healthy human eyes, this flow averages 2.75 μL per minute.^{53,54} This decreases by only about 30% during a lifetime and is the same for males and females. In the course of a day, the lowest flow rate, 1.2 μL per minute, occurs at night. This rate more than doubles to 3.0 μL per minute during the morning hours.^{55,56}

CONTROVERSY

Although epinephrine and norepinephrine can increase aqueous humor formation in the human eye, alterations in these substances do not fully account for the suppression of aqueous humor flow during sleep.

The magnitude of the suppression of aqueous flow during sleep is as great as the inhibitory effects by any pharmacological agent used for the treatment of glaucoma. The mechanisms that control this aqueous flow suppression are only partly understood and are still under investigation. Studies of catecholamines have found that epinephrine and norepinephrine are the only hormones or neurotransmitters that consistently increase aqueous formation in human eyes.⁵⁷ In patients without adrenal glands, and hence without circulating epinephrine, the normal rhythm of aqueous flow is maintained,⁵⁸ indicating that epinephrine cannot be solely responsible for the circadian rhythm of aqueous flow. Corticosteroids have no direct effect on aqueous flow, but when given in conjunction with epinephrine, they appear to augment the effect of the catecholamine.⁵⁹ At present, it is believed that endogenous catecholamines stimulate aqueous flow during the daytime by reaching ocular receptors via the general circulation or via sympathetic nerve terminals. Absence of these stimuli is a possible cause of the lower rate during sleep. Much more research is needed to understand the normal control of aqueous humor formation and, thus, IOP.

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ANATOMY AND PHYSIOLOGY OF AQUEOUS HUMOR OUTFLOW

John C. Morrison, M.D. and Ted S. Acott, Ph.D.

Intraocular pressure (IOP) is determined by the balance between aqueous humor production and outflow. With the exception of circadian oscillations of aqueous production, most alterations in IOP result from a change in the resistance to aqueous outflow. Understanding the anatomy of aqueous outflow and the factors that affect this resistance is essential to understanding many forms of glaucoma and their treatment.

Aqueous outflow occurs through both conventional and unconventional routes. In the former, aqueous moves through the trabecular meshwork and into Schlemm's canal, and from there to episcleral veins via collector channels that traverse the limbal sclera. Unconventional outflow occurs through the base of the ciliary body, probably in between ciliary muscle fibers, and into the supraciliary and suprachoroidal space. From there, aqueous escapes through the sclera via emissary canals that contain ciliary nerves, perforating ciliary vessels and vortex veins. Most of our knowledge of aqueous humor outflow in the normal eye is based on our understanding of factors that modulate the conventional system. The recent development of drugs that specifically improve uveoscleral outflow, however, has increased our interest in unconventional outflow and how it can influence IOP.

The physiology of conventional aqueous humor outflow differs from unconventional outflow in several important ways. The former is diminished by increased IOP, but the latter appears to be pressure independent. Although increased ciliary muscle tone improves conventional outflow, it diminishes uveoscleral outflow. However, in both pathways, extracellular matrix (ECM) appears to contribute to aqueous humor outflow resistance. Outflow through the juxtaganular region of the trabecular meshwork into Schlemm's canal is as yet incompletely understood. Evidence for both intracellular and intercellular transport exists, and, although transport appears to be primarily passive, active processes may also contribute.

ANATOMY OF AQUEOUS HUMOR OUTFLOW

CONVENTIONAL (CANALICULAR, TRABECULAR) AQUEOUS OUTFLOW

Conventional aqueous humor outflow begins with the trabecular meshwork. Viewed in cross section, the trabecular meshwork is a triangular, porous structure that spans the opening of the internal scleral sulcus and overlies Schlemm's canal. (Figs. 4–1A, B; 4–2A, B) The trabecular meshwork has three components: the uveoscleral, corneoscleral, and juxtaganular meshwork.

Uveoscleral Meshwork

The uveoscleral meshwork lies most internal, forming the lateral border of the anterior chamber. It consists of thick bands of connective tissue that are covered with endothelium, with large intervening spaces that measure between 25 and 75 µm. These cordlike bands originate from the root of the iris, forming a network anterior to the scleral spur that inserts at Schwalbe's line, the peripheral termination of Descemet's membrane. The ECM of the uveoscleral meshwork beams includes interstitial collagen with intermixed elastin fibrils.^{1,2} The endothelial lining is continuous with that of the corneoscleral meshwork and has similar characteristics, described in the following text.

Corneoscleral Meshwork

The corneoscleral meshwork makes up the middle and most extensive portion of the trabecular meshwork. This consists of connective tissue plates with a complex ECM similar to that of the uveoscleral meshwork. Interspersed with the collagen are fibrils with a structure like that of

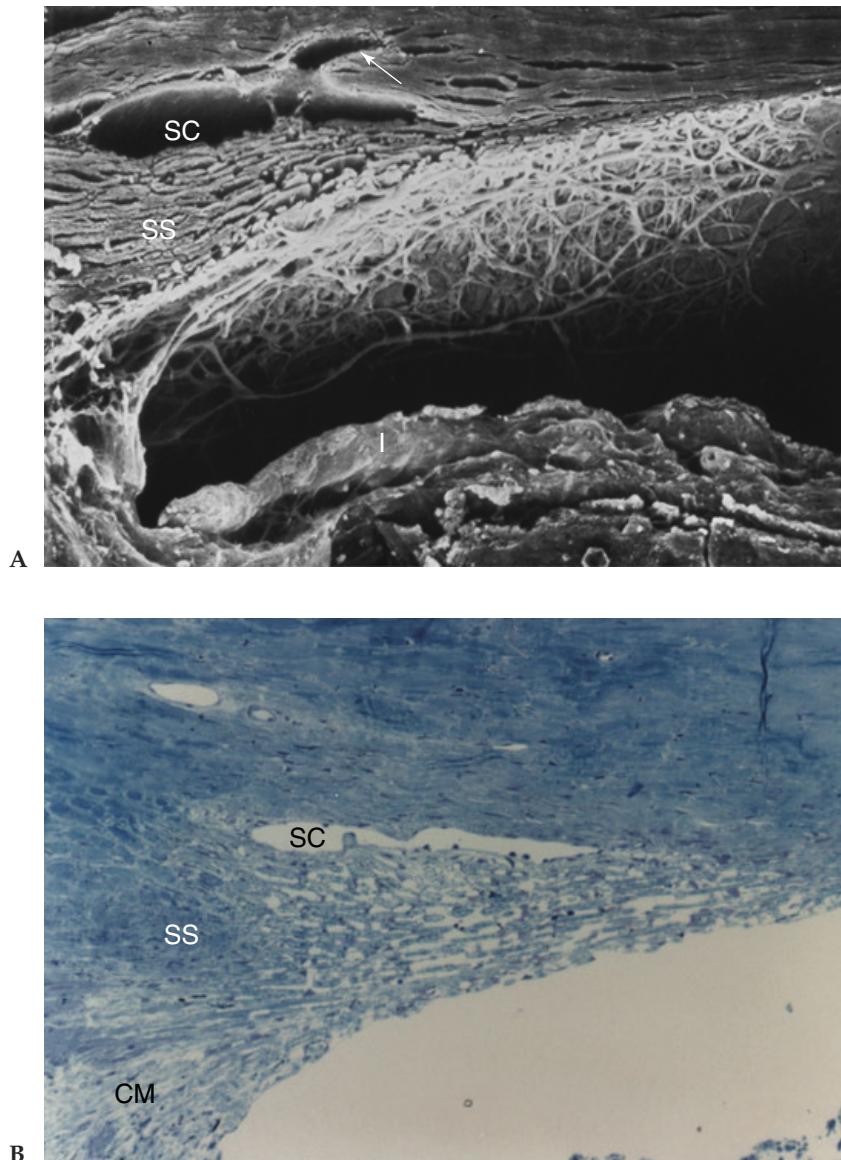


FIGURE 4-1 Anterior chamber angle of the normal human eye, viewed by (A) scanning electron microscopy and (B) light microscopy. The trabecular meshwork spans the scleral sulcus, originating from the scleral spur (SS) to insert into the peripheral cornea. In (A) the cordlike appearance of the uveoscleral meshwork is readily seen spanning the innermost portion of the meshwork. In (B) note that some of the corneoscleral meshwork originates from the longitudinal fibers of the ciliary muscle. SC, Schlemm's canal; arrow, collector channel; CM, Ciliary muscle; I, iris root. (Reproduced (A) with permission from W.B. Saunders Co. and (B) courtesy of Douglas Johnson, M.D.)

elastin, presumably to provide resilience to the tissue to accommodate tissue stretching that results from periodic changes in IOP. The connective tissue plates arise primarily from the scleral spur and extend over the internal scleral sulcus, inserting along the anterior region of the sulcus. Some of the corneoscleral meshwork arises from tendons of the longitudinal ciliary muscle fibers (Fig. 4-1B).

The outer layers of these connective tissue bands become progressively more sheetlike, the closer they are to Schlemm's canal. These sheets contain round or oval pores that gradually decrease from approximately 50 µm down to 5 µm in diameter as they approach Schlemm's canal. Endothelial cells lining these structures rest upon a basement membrane and are interconnected by desmosomes and gap junctions.³ Tight junctions do not exist between these cells, however, and aqueous humor can apparently pass freely between them. These endothelial cells also have

been shown to contain intermediate, actin-like filaments that may be important for cell motility and phagocytosis.⁴

Juxtaganicular Meshwork

The outermost, or juxtaganicular, region of the trabecular meshwork is thought to provide much of the resistance to aqueous humor outflow (Fig. 4-2B). This consists of a single, amorphous layer of tissue that borders Schlemm's canal. Its inner endothelial layer is continuous with that of the corneoscleral meshwork, and it has similar features. The connective tissue core of the juxtaganicular meshwork also comprises a complex ECM and contains a few juxtaganicular cells embedded completely within it. The ECM includes amorphous basement membrane materials, as well as sheaths that surround what are felt to be elastic tendons (Fig. 4-2B).

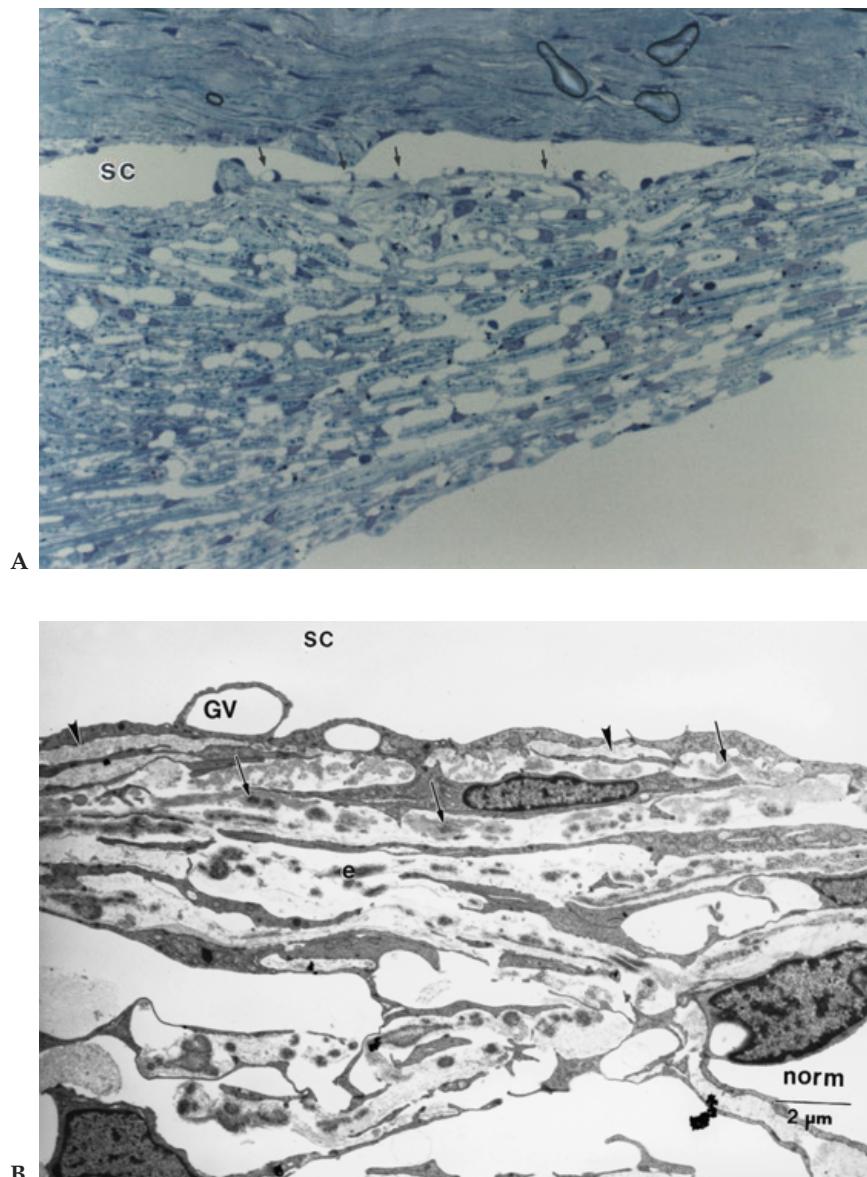


FIGURE 4-2 (A) High-power light micrograph of the trabecular meshwork shows the innermost uveoscleral meshwork, the middle corneoscleral meshwork, and the outermost juxtaganular meshwork, which forms the inner wall of Schlemm's canal (SC) and possesses giant vacuoles (arrows). (B) Transmission electron micrograph of juxtaganular meshwork shows giant vacuoles (GV) projecting into Schlemm's canal. Immediately beneath the inner wall of Schlemm's canal is a light gray amorphous material with properties of basement membrane (arrowheads). Arrows indicate sheaths around elastic tendons (e). Both of the latter findings are increased in specimens with primary open-angle glaucoma. (See also Fig. 15-1). (Courtesy of Douglas Johnson, M.D.)

The outermost portion of the juxtaganular meshwork consists of a layer of endothelial cells that form the inner wall of Schlemm's canal. These cells, which also contain actin filaments, possess variable numbers of large, or giant, vacuoles that project into Schlemm's canal, and small pores measuring approximately $1 \mu\text{m}^{5,6}$ (Figs. 4-3A,B). These features, plus the endothelial cell nuclei, give the surface of the inner wall of Schlemm's canal an irregular appearance that is distinctly different from that of the outer wall. Intercellular junctions have been demonstrated between these endothelial cells, and these restrict, to some degree, aqueous flow from the trabecular meshwork into Schlemm's canal.^{3,7} Other analyses of the cells lining Schlemm's canal show that they are significantly different from cells of the trabecular meshwork.⁸⁻¹¹

Viewed from within, the outer wall of Schlemm's canal is, by contrast, generally smooth. It contains scattered, large openings of aqueous collector channels. Through these channels, aqueous traverses the limbal sclera to empty into the episcleral veins and then to the ophthalmic veins and the general circulation.

UNCONVENTIONAL (EXTRACANALICULAR, UVEOSCLERAL) AQUEOUS OUTFLOW

This route of aqueous outflow encompasses all pathways that do not initially involve the trabecular meshwork. Small quantities of aqueous humor probably diffuse anteriorly through the cornea, and posteriorly into the vitreous and out of the eye through the retina or optic nerve head. However, the bulk of this extracanalicular outflow

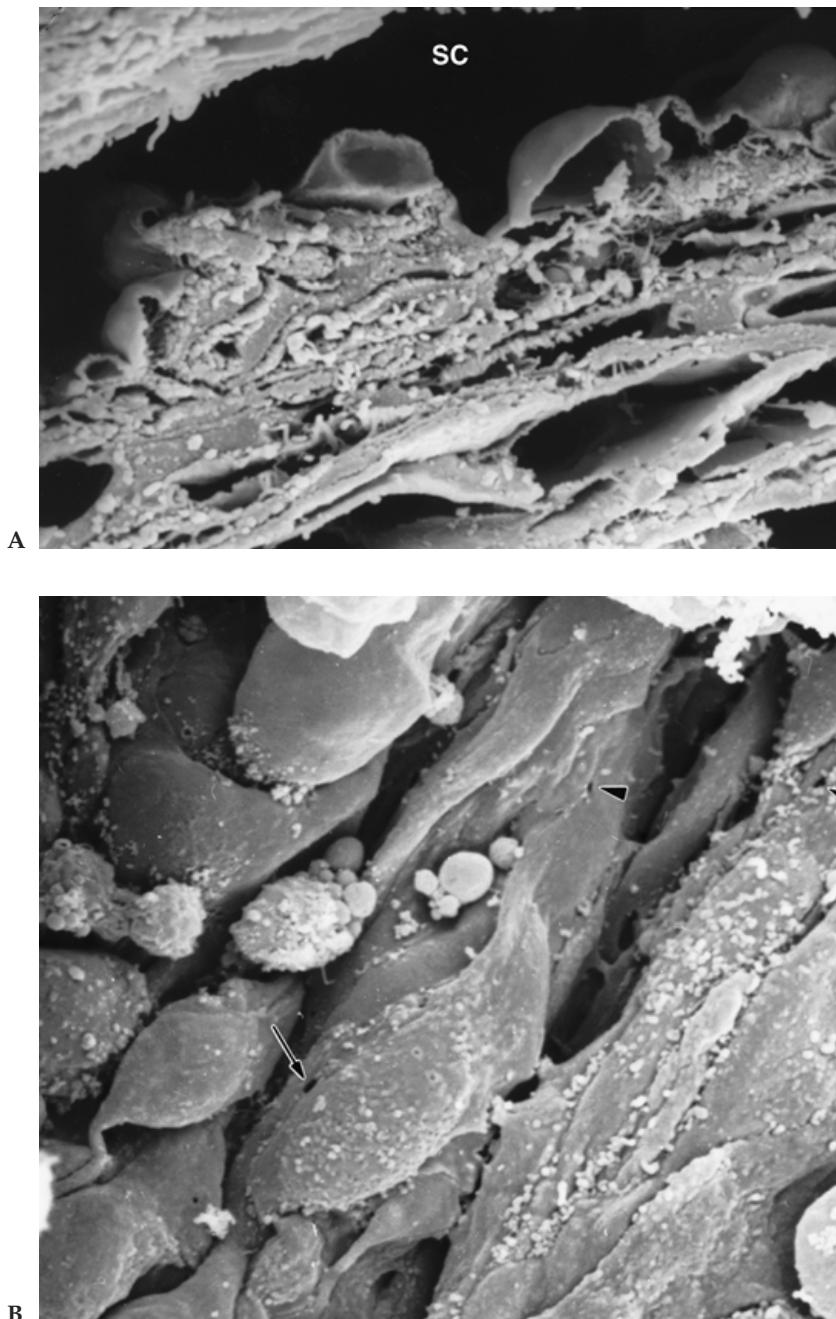


FIGURE 4-3 Scanning electron micrographs of juxtaganular meshwork, viewed in (A) cross section, showing giant vacuoles, and (B) from within Schlemm's canal, demonstrating numerous bulges into the canal, representing either giant vacuoles or cell nuclei. Arrow indicates a pore at the base of a giant vacuole. Arrowhead indicates other pores, not associated with giant vacuoles. (Courtesy of Douglas Johnson, M.D.)

occurs through the anterior uvea. For this reason, it is often referred to as uveoscleral outflow.

Uveal aqueous humor outflow was first demonstrated by Bill in 1965.¹² He showed that a large portion of radiolabeled albumen injected into the anterior chamber of monkey eyes later appeared in the uvea and sclera. This pathway most likely begins at the base of the ciliary muscle, which does not present an epithelial barrier to the anterior chamber. This region is identifiable gonioscopically as the ciliary body band.¹³ Aqueous probably flows within the loose connective tissue that exists between the fibers of the longitudinal portion of the ciliary muscle. These fibers insert posteriorly into the connective tissue of

the suprachoroidal space. From here, aqueous can escape either directly through the sclera, which is composed primarily of collagen and fibroblasts, or into the episcleral space via emissary canals through the sclera.

Tracer studies using different size materials have confirmed these pathways, suggesting some differences, depending on the particle size. Small molecules, such as fluorescein, readily pass from the anterior chamber into the suprachoroidal space.¹⁴ These can also penetrate into the vessels of the iris and ciliary body, leading to the vortex veins. This forms another potential outflow pathway, termed the uveovortex pathway, the relative importance of which is poorly understood.¹⁵ In primates, larger

particles, including 1 µm latex spheres, can rapidly pass from the anterior chamber into the suprachoroidal space, even to the posterior region of the eye. These have been shown to exit the sclera through the perforating emissary canals around the ciliary vessels and nerves.¹⁶

PHYSIOLOGY OF AQUEOUS HUMOR OUTFLOW

IOP is determined primarily by the resistance to aqueous humor outflow. In the normal eye, this resistance appears to be dictated by several factors. These factors may be extrinsic or intrinsic to the aqueous humor outflow pathways. Extrinsic factors include IOP and ciliary muscle contraction. Intrinsic factors include both the direct activity of trabecular meshwork cells and the indirect effects of cellular activity, such as in maintaining the ECM of both the trabecular meshwork and the ciliary body, which then provides resistance to outflow. The relative influence of these direct and indirect cellular factors is currently under debate.

INTRAOCULAR PRESSURE

In enucleated human and monkey eyes, increased IOP appears to immediately diminish aqueous humor outflow facility.^{17,18} This appears to be due primarily to collapse of the trabecular meshwork into Schlemm's canal at the higher pressures.^{17,19} Uveoscleral outflow, by contrast, is relatively independent of IOP in normal eyes.²⁰

Experiments with perfused human anterior segment organ cultures show that increasing the perfusion rate will produce an elevated IOP. Interestingly, this elevated IOP slowly returns to normal over several days, even though the increased perfusion rate is sustained.²¹ This homeostatic IOP regulatory mechanism suggests that trabecular cells can sense the juxtaganular ECM distortion produced by elevated IOP and they can respond by increasing ECM turnover in this region.^{21,22}

CILIARY MUSCLE TONE

Contraction of the ciliary muscle has long been known to influence aqueous humor outflow through conformation effects on the trabecular meshwork (see Chapter 34).²³ Pharmacological cycloplegia may reverse this effect, increasing aqueous humor resistance within the conventional outflow pathway and increasing IOP.²⁴

By contrast, pharmacological manipulation of ciliary muscle contraction has the opposite effect on uveoscleral outflow. Here, contraction of the ciliary muscle through the use of cholinergic agonists diminishes uveoscleral outflow,²⁵ whereas cycloplegia improves outflow through this pathway.^{26,27} These effects appear to be mediated, at least in part, by either decreased or increased space

between the ciliary muscle fibers due to contraction or relaxation of the fibers.

EXTRACELLULAR MATRIX

The ECM materials within the trabecular beams and particularly within the juxtaganular meshwork, as well as on the surface of trabecular endothelial cells has long been suspected of contributing to outflow resistance. This was initially suggested by the observation that perfusion of enucleated monkey and canine eyes resulted in increased outflow facility over time.²⁸ This "wash-out" effect is not observed in human eyes.²⁹ However, perfusion of enucleated or cultured human or other animal eyes with different glycosaminoglycan-degrading enzymes generally removes approximately 50% of the outflow resistance.^{30–33} Proteoglycans, with its large and numerous negatively charged glycosaminoglycan side-chains, are thus a likely source of at least a portion of the outflow resistance.

Experiments with anterior segment organ cultures have shown that both perfusion and induction of trabecular matrix metalloproteinases, the enzymes normally responsible for initiating ECM turnover, can reversibly increase outflow facility.²² Similarly, selective inhibition of the endogenous matrix metalloproteinases also reversibly reduces outflow facility. This suggests that ongoing ECM turnover is critical for the homeostatic maintenance of the normal outflow resistance.

The ECM appears also to play a role in modifying aqueous humor outflow through the unconventional pathway. Although reduced IOP that accompanies uveitis results, at least in part, from reduced aqueous humor production, alterations in ciliary body ECM have also been observed in ocular inflammation.³⁴ The potent prostaglandin analogs (see Chapter 35) appear to improve uveoscleral outflow primarily by altering the ECM composition of the ciliary body.³⁵

TRANSPORT THROUGH THE JUTXACANALICULAR MESHWORK

Most investigators feel that the juxtaganular region of the meshwork is a major site of aqueous humor outflow resistance. However, the exact route by which aqueous moves into Schlemm's canal remains controversial. The presence of pores and giant vacuoles within the endothelial cells of the inner wall of Schlemm's canal discussed above has been interpreted by many investigators as representing a transcellular pathway of fluid movement. In support of this, tracer materials injected into the anterior chamber have been found within these vacuoles, and the pores appear to provide communication between the intertrabecular spaces and Schlemm's canal.^{36,37} These vacuoles may represent a dynamic system, intermittently opening and closing. The number and size of these vacuoles increase with increasing

IOP, further supporting the idea that this is a passive, not an active, metabolic process.^{17,19} However, recent studies attempting to determine the significance of the smaller vacuoles and of the giant vacuoles on Schlemm's canal endothelium, either as a source of resistance or as an indicator of flow rates, have further supported a correlation but not a simple predictive relationship.³⁸⁻⁴¹

Other studies suggest that aqueous humor may also traverse the juxtaganular meshwork by an intercellular pathway. Following injection of tracer substance into the anterior chamber, the material can be found in clefts between endothelial cells.⁴² These clefts are also increased at higher perfusion pressure. Currently, it is unknown which of these pathways is predominant, and interpretation of the morphological findings may be limited by fixation artifacts.

Recently, a number of studies have provided evidence that trabecular meshwork cells may have a rapid, direct, cellular role in aqueous outflow resistance. This appears to occur through changes in cell shape induced by alterations of the cytoskeleton and matrix attachments of endothelial cells lining the inner wall of Schlemm's canal, as well as those within the trabecular meshwork.⁴³⁻⁴⁷ As discussed in Chapter 18, effects such as these may mediate steroid-induced glaucoma. The exact mechanisms of how these cellular changes modulate outflow facility is still under investigation. The idea that a funneling effect could explain a portion of this effect has also been proposed.⁴⁸

Several studies have been performed to correlate the morphological appearance of the juxtaganular meshwork with physiological measurements of aqueous flow.⁴⁹⁻⁵¹ The calculated resistance is consistently considerably greater than that presented by identifiable ultrastructural components. This has been interpreted to mean that the remainder of the resistance is due to glycosaminoglycans or similar materials that are not sufficiently electron-dense to detect. Studies utilizing newer methods of tissue preparation, as illustrated in Figure 4-4, may help resolve this uncertainty.

CONTROVERSY

Ultrastructural evidence of aqueous humor outflow resistance within the trabecular meshwork does not appear to account for all of the resistance calculated from physiological studies.

RELATIVE IMPORTANCE OF CONVENTIONAL AND UNCONVENTIONAL OUTFLOW

Early studies of the unconventional pathway of aqueous humor outflow performed in monkeys revealed an outflow rate of between 0.2 and 1.0 μL per minute.⁵² This represents approximately 50% of total outflow facility. Initial,

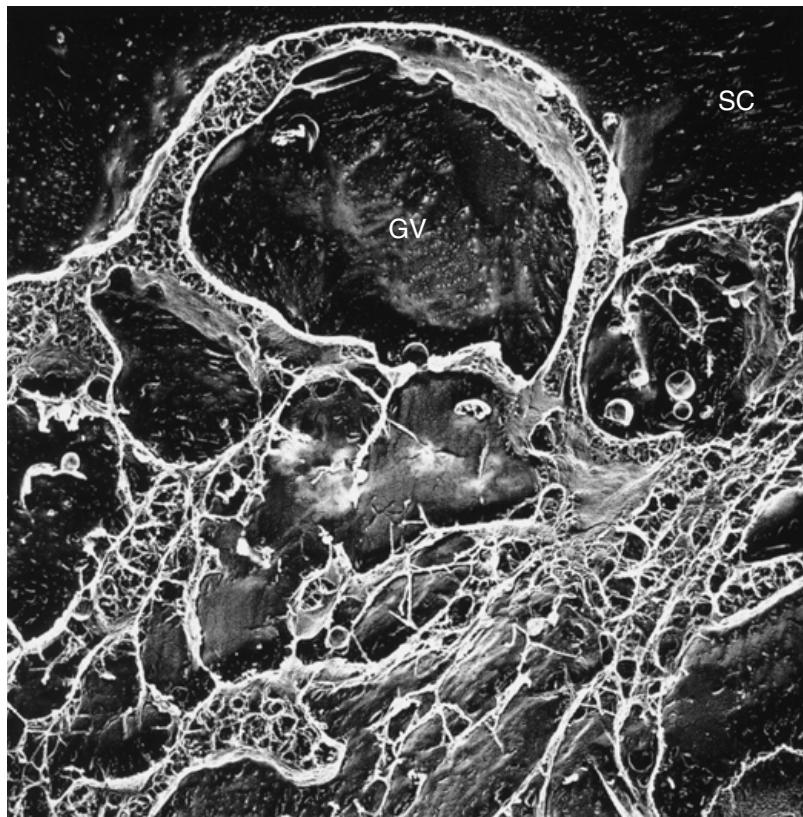


FIGURE 4-4 Electron micrograph of juxtaganular meshwork, viewed after quick-freeze, deep-etch preparation, which avoids standard histologic dehydration. Note giant vacuole (GV) projecting into Schlemm's canal (SC). Cellular and intercellular tissues that may contribute to aqueous outflow resistance are better preserved with this type of preparation. (Courtesy of H. Gong, M.D., Ph.D., and T. Freddo, O.D., Ph.D.)

limited direct measurements in two nonglaucomatous human eyes showed that uveoscleral outflow was 0.1 and 0.3 µL per minute, or only 4% and 14% of total outflow.²⁷ However, more recent work using indirect measurements demonstrates that this pathway is dependent on age. In younger individuals, uveoscleral outflow appears to account for as much as 54% of total outflow, as compared with 46%, measured in subjects older than 60 years.⁵³ Overall aqueous humor production was also found to be less in older individuals, 2.4 versus 2.8 µL per minute.

SPECIAL CONSIDERATION

The contribution of unconventional outflow to total aqueous humor outflow generally decreases with age.

Comparisons between conventional and unconventional outflow must always be interpreted in light of the level of IOP. Whereas the former is affected by IOP, the latter is not, and is considered pressure independent. In addition, agents that alter ciliary muscle tone, discussed earlier, will also affect the relative contribution of the conventional and unconventional routes to total aqueous humor outflow.

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GONIOSCOPY

Julia Whiteside-Michel, M.D.

Gonioscopy allows the clinician to examine the anterior chamber angle and is an essential step in the evaluation of every glaucoma patient. Relying on a contact lens to overcome total internal reflection, this technique can reveal normal and abnormal variations in angle anatomy that might not be visible by slit-lamp examination alone.

The examiner can perform either direct or indirect gonioscopy. The former technique is less likely to produce artifactual distortions in the angle appearance and is well suited to examining supine and anesthetized patients. However, this method requires equipment not widely available in a routine clinical practice.

The primary purpose of gonioscopy is to determine whether a patient has open-angle or angle-closure glaucoma. With a systematic technique that documents the appearance of the normal angle structures and the presence of specific angle abnormalities, gonioscopy is also an indispensable aid to the diagnosis of a wide range of primary and secondary glaucomas.

GONIOSCOPIC APPEARANCE OF THE ANTERIOR CHAMBER ANGLE

The anterior chamber “angle” is created by two lines, one tangent to the trabecular meshwork and the other along the iris plane. The term is used to describe the region where the aqueous outflow system lies. It normally consists of four main structures, from anterior to posterior (Fig. 5–1A).

1. *Schwalbe's line*. This structure represents the peripheral edge of Descemet's membrane and consists of a thickening or ledge of tissue where the inner cornea and sclera meet, with their different radii of curvature. It generally appears as a white line or ridge and borders the anterior trabecular meshwork.

2. *Trabecular meshwork*. This sievelike ring of tissue is the site of conventional aqueous humor outflow. It is lightly pigmented anteriorly, and usually darker gray or brown posteriorly over Schlemm's canal, where there is presumably higher aqueous flow and greater deposition of pigment.
3. *Scleral spur*. This is formed by a projection of circumferential collagen fibers from the inner sclera and represents the posterior boundary of the inner scleral sulcus, in which Schlemm's canal rests. This structure also provides the anterior insertion of the longitudinal ciliary muscle fibers and is the origin of the corneoscleral meshwork. Although the scleral spur is identifiable as a white band just posterior to the pigmented meshwork, its color is typically light gray or off-white because of overlying fibers of the uveoscleral meshwork.
4. *Ciliary body band*. This represents the anterior aspect of the ciliary muscle, into which the iris root inserts in most normal individuals. It typically appears dark gray or brown and lies just posterior to the scleral spur.

Clinically, the anterior chamber angle cannot be seen by direct inspection because light leaving the angle is reflected back into the eye by the air–cornea interface. All gonioscopy lenses are designed to overcome this total internal reflection and exceed the critical angle of the cornea by altering the corneal air–fluid interface. Some of these lenses provide a direct view of the angle, but most use an indirect approach with the aid of an internal mirror.

The anterior chamber angle structures first should be examined with sufficient illumination to allow their identification. In cases with an unusual angle appearance or lack of pigmentation, the meshwork often can be identified by its ground glass appearance, best seen with sclerotic scatter. In the horizontal regions, this may

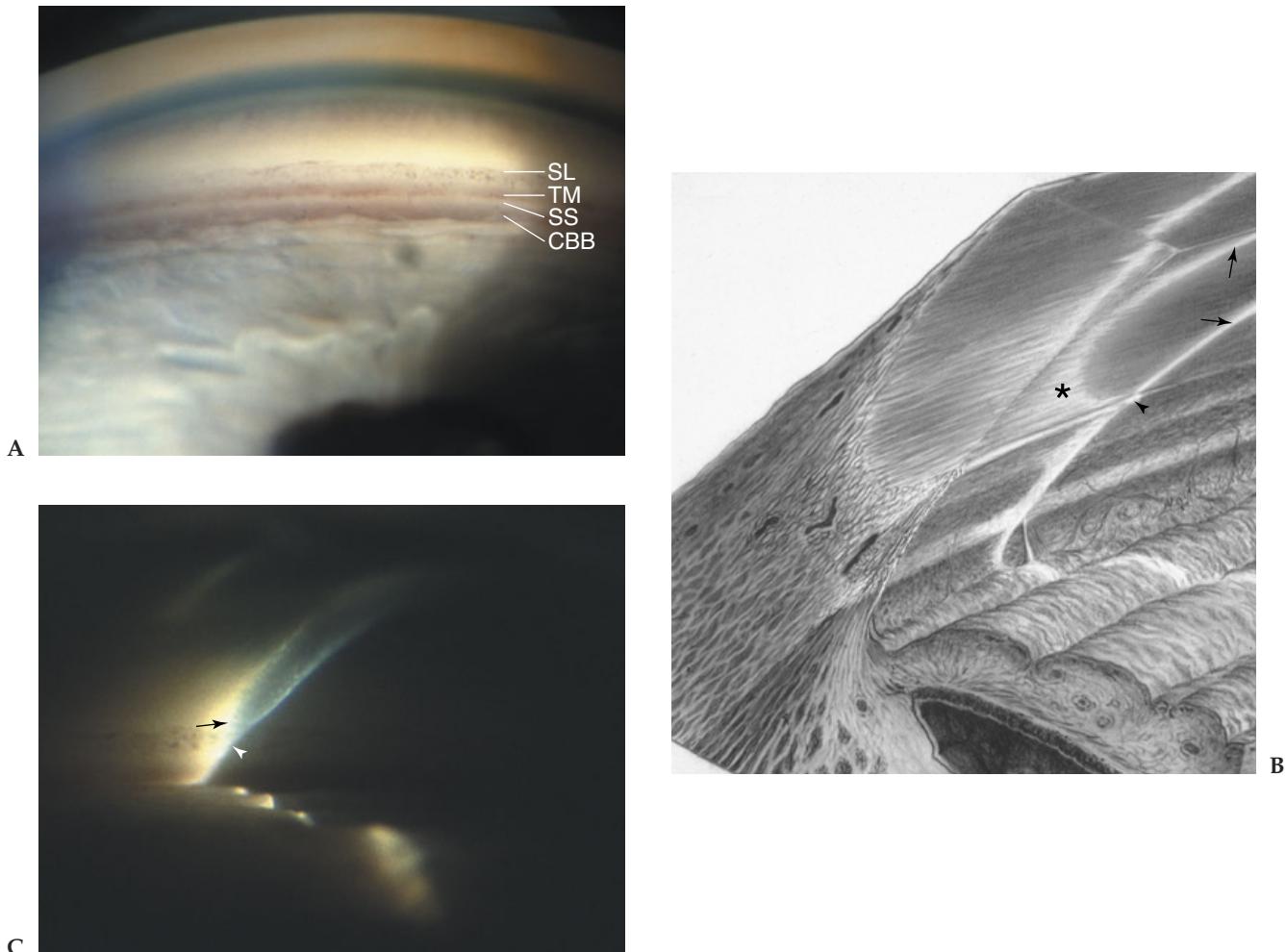


FIGURE 5-1 (A) Gonioscopic appearance of the normal anterior chamber angle. Schwalbe's line (SL), trabecular meshwork (TM), scleral spur (SS), and ciliary body band (CBB) all are visible in this open angle. (B) Drawing of the microscopic cross-section of the anterior chamber angle combined with the gonioscopic view to illustrate the anatomic basis for the corneal parallelepiped and the corneal light wedge. The parallelepiped (arrows) is formed by light reflecting from the anterior and posterior corneal surfaces. At the peripheral cornea, the outer margin of the parallelepiped curves posteriorly as the slit beam illuminates the junction of the clear cornea with the opaque sclera. This curved line forms the base of the corneal light wedge (asterisk). The point at which this base meets the inner, endothelial margin of the parallelepiped corresponds to Schwalbe's line (arrowhead). (C) Goniophotograph using a thin slit beam illustrating the base of the corneal light wedge (arrow) and Schwalbe's line (arrowhead). (Drawing by Lee Allen, copyright the University of Iowa. From Alward WLM. *Color Atlas of Gonioscopy*. Barcelona: Wolfe; 1994. Courtesy of W.L.M. Alward, M.D.)

be seen more easily by directing the slit beam anteriorly. The examiner usually can locate Schwalbe's line also, by using the parallelepiped and corneal light wedge, and then deducing the identity of other visible angle structures.^{1,2}

The corneal parallelepiped is identified in the peripheral cornea as two curved, parallel and then converging lines, representing light reflecting from the corneal epithelium and endothelium. In the superior and inferior mirrors, this is best seen by angling the slit beam 30 to 60 degrees from the viewer's gaze. With some slit-lamps, this can be created also in the nasal and temporal mirrors

by tilting the light arm forward and rotating the slit beam to the horizontal position.

At the peripheral cornea, where the corneal epithelium and endothelium end, these two light beams meet because the limbal sclera is not transparent (see Fig. 5-1B,C). By using a thin slit beam, properly oriented with the focal plane of the oculars, the examiner will see that the outer, epithelial margin of the parallelepiped curves posteriorly to meet the inner, endothelial margin. This line, which has a U- or V-shaped configuration, represents the interface between the clear cornea and opaque sclera. It also forms the base of a wedge-shaped band of light, termed the

corneal light wedge. The point at which the base of the corneal light wedge meets the endothelial line of the parallelepiped is a reliable indicator of Schwalbe's line. Posterior to this point, only one slit beam line will be seen on the surface of the anterior chamber angle structures. In some eyes, this subtle but important phenomenon is easier to see with the Goldmann lens.

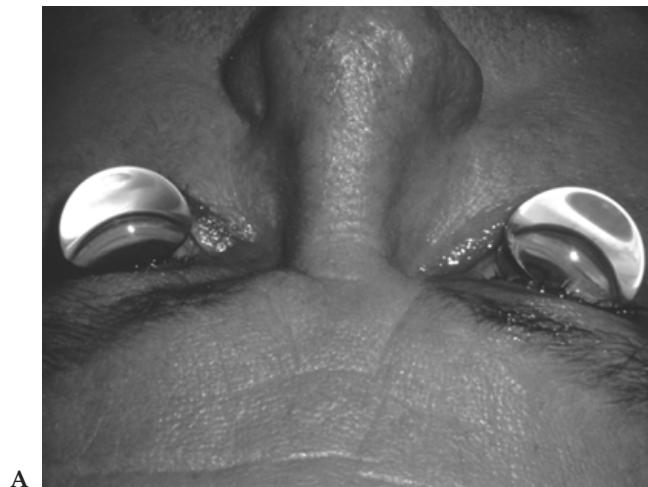
PEARL... If the view of the anterior chamber angle is confusing, the one structure that can be definitively identified is Schwalbe's line, located where the anterior margin of the parallelepiped meets the posterior margin at the base of the corneal light wedge.

DIRECT GONIOSCOPY

Direct gonioscopy allows the examiner to inspect the anterior chamber angle with only mild deviation of the light path. Direct gonioscopy is usually performed with a Koeppe lens, a hand-held Barkan or transillumi-

nator light source, and a stereoscopic viewer (Haag-Streit M10900568, Bern, Switzerland)^{3,4} (Fig. 5–2A,B). The Koeppe lens, made of barium crown glass or plastic, has an inner radius of curvature of 7.5 mm, and an outer radius of 12.5 mm. The weight of the viewer can be counterbalanced by a weight attached to the opposite end of a cord or wire suspended from the ceiling through a pulley system.⁵ With the patient in the supine position, saline is used to fill the space between the lens and the cornea.^{6,7} The examiner inspects the different angle structures by altering the angle of view, without manipulating the lens or asking the patient to change fixation.

The Koeppe lens itself magnifies the image 1.5×, whereas the stereoscopic viewer provides 10× or 16× magnification, depending on the oculars used. Koeppe lenses are available in sizes ranging from 16 to 22.5 mm in diameter. Most adults can be examined with the 16 or 18 mm lens,^{4,8} but a larger-diameter lens should be used if the limbus is irregular or a filtering bleb is present.⁹ Other examples of direct gonioscopy lenses are the Swan-Jacob and the Hoskins-Barkan surgical contact lens. These are designed primarily for performing a goniotomy through the surgical microscope, although



A



B

FIGURE 5-2 Direct gonioscopy. (A) Bilateral Koeppe lenses in place. (B) Koeppe gonioscopy with Haag-Streit stereoscopic viewer suspended from the ceiling.

they can also be used to examine a sedated child with a portable slit-lamp.

The advantage of direct gonioscopy is that it can be performed on patients under anesthesia and does not rely on patient cooperation. In addition, angle structures viewed in this manner are most likely to be seen in their natural state because the lens is unlikely to exert unusual compression on the eye. A possible disadvantage is that the angle may appear more open with the patient in the supine rather than the sitting position, because of the effect of gravity on the iris, lens, and ciliary body. Direct gonioscopy is not widely performed in routine clinical practice because the equipment is not readily available to the average clinician and the procedure itself is less convenient than indirect gonioscopy methods.

INDIRECT GONIOSCOPY

Indirect gonioscopy is performed at the slit lamp with a Goldmann, Zeiss, or similar lens (Fig. 5–3A,B). With all of these lenses, the slit-lamp provides excellent magnification and facilitates identification of abnormal structures. All indirect lenses utilize mirrors to reflect light into, and the image out of, the angle, creating an inverted image. The distance between the mirror and the central cornea will influence the appearance of the angle⁷ (Table 5–1).

The Goldmann-type lenses require methylcellulose or a viscous artificial tear gel to occupy the space between the cornea and lens. Although saline can be used in some patients, this produces an abnormally strong suction between the lens and cornea and can lead to a corneal abrasion when the lens is removed. The most commonly used variations of these lenses include the Goldmann single- and three-mirror lenses, the Thorpe lens, and the Ritch lens.

One advantage of these lenses is that, with rotation, they allow a continuous view of the entire angle circumference. In addition, because these are used for argon laser trabeculoplasty, this view helps predict the feasibility of performing this procedure. Finally, the large diameter (12 mm) the small central radius of curvature of these lenses minimizes the chance of inadvertently and indenting the angle open. These gonioscopy lenses, however, generally cannot be tilted with respect to the visual axis without indenting the sclera and falsely closing the angle. They also can create a vacuum effect and falsely open the angle. These lenses are not now widely used for routine examination because of the relative inconvenience of using a viscous fluid interface, that can blur the patient's vision. However, artificial tear saline is often used instead of more viscous fluids.

In contrast, the Zeiss lens and newer, altered Posner and Sussman models utilize the patient's tear film as an interface between the lens and cornea. Because of their smaller central diameter (9 mm), these lenses can be tilted

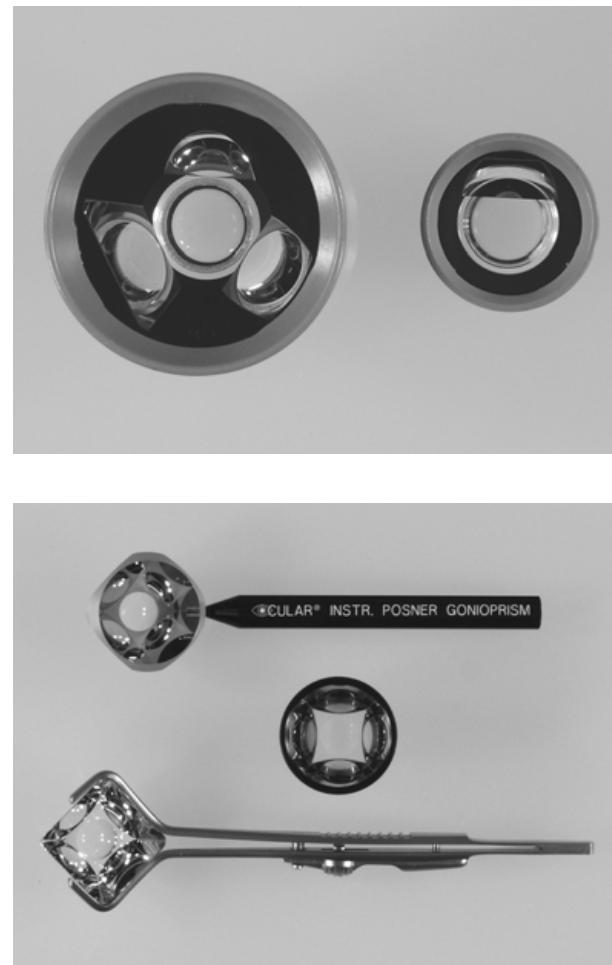


FIGURE 5-3 Indirect gonioscopy lenses. (A) Goldmann 3-mirror and 1-mirror lenses (left to right). (B) Posner, Sussman, and Zeiss lenses (top to bottom).

and moved relatively easily over the surface of the cornea, often with the patient altering his gaze, to facilitate the examination of narrow or suspicious anterior chamber angles. In addition, the examiner can apply pressure and use these lenses for corneal indentation. Indentation gonioscopy and other maneuvers for examining a narrow angle are discussed further in the next section.

PITFALL... When performing gonioscopy with a Zeiss, Posner, or Sussman lens, the clinician must avoid inadvertent corneal indentation, which can produce corneal striae and falsely open the angle.

The major challenge of using these lenses lies in creating sufficient fluid contact to provide an adequate view, without pressing on the eye and distorting the appearance of the angle. Corneal wrinkles or folds in Descemet's membrane should alert the examiner to inadvertent corneal indentation during gonioscopy. To prevent this

TABLE 5-1 INDIRECT GONIOSCOPY LENSES

<i>Lens</i>	<i>Dimensions</i>	<i>Mirrors</i>
Goldmann-type lenses		
Goldmann 1-mirror	12 mm diameter 1.5 mm flange width	12 mm high, 9 mm wide 3 mm from center Light strikes 6 mm from corneal apex Angle 62 degrees
Goldmann 3-mirror	12 mm diameter 3 mm flange width	10–12 mm high, 9 mm wide Effective field: 80 degrees 7 mm from center Light strikes 11.5 mm from corneal apex
Thorpe		Four 62-degree mirrors Angle 59 degrees (gonioscopy lens)
Ritch	12.5 mm diameter	Two 64-degree mirrors (superior angle viewing) 67 degrees and 73 degrees (retina lenses) Effective field: 90 degrees Two 59-degree mirrors (inferior angle viewing) 17D plano-convex button over two mirrors (1.4X magnification)
Indentation lenses		
Zeiss	9 mm diameter Inner radius 7.85 mm	12 mm high 5 mm from center Angle 64 degrees
Posner	9 mm diameter Inner radius 8.13 mm High-impact plastic	Angle 64 degrees
Sussman	Same as Posner, without handle	Angle 64 degrees

possibility, the examiner should develop the habit of frequently breaking and then making contact with the cornea. This helps maintain just enough pressure to create the contact, but no more.

Air bubbles in the lens–cornea interface suggest either insufficient contact in eyes with relatively steep or flat corneas, or an inadequate tear film. The Posner and Sussman lenses have a flatter inner surface with a larger radius of curvature than that of the Zeiss lens. Although these lenses are less likely to trap air bubbles when placed on relatively flat corneas, they require central corneal indentation to create complete contact when applied to steep corneas. A drop of methylcellulose, saline, or artificial tears used in the cup of any of these lenses often makes it easier to get a clear image without indenting the cornea.

If the ciliary body band is not seen in an adult, this suggests either an angle anomaly, a normal variant, or some form and degree of angle closure. This can be influenced by both physiological and pharmacological pupil dilation. In darkness, the iris shortens and thickens, its anterior convexity increases, and the angle narrows.^{10–12} Pupil constriction from light reaction or accommodation can stretch the iris away from the angle structures and open the angle.^{10,11} To avoid light-induced pupil constriction, the angle must be examined while the pupil is physiologically dilated.¹³ This is accomplished by illuminating the angle with a small circle or short column of light,^{13–17} without directing it across the pupil or toward the fundus. If the angle is not examined under the condition of physiological pupillary dilation, the clinician can misinterpret an angle as narrow, but not occludable.

TECHNIQUES FOR ASSESSING ANGULAR WIDTH BY GONIOSCOPY

One of the major purposes of gonioscopy is to assess the width of anterior chamber angle and determine the patient's risk of developing acute or chronic angle closure, or the extent of angle closure already present. Several specific techniques are helpful in making this assessment.

SPECIAL CONSIDERATION

Evaluating an angle for potential occludability requires a dark room and a small beam of light directed into the angle to prevent light-induced pupil constriction, which may artifactually open the angle.

Several other physiological factors also can change the configuration of the angle. Parasympathetic stimulation can cause mild shifting forward of the iris-lens diaphragm, and sympathetically stimulated dilation can produce additional bunching of the iris into the angle. Both of these can affect the clinician's ability to assess the possible risk of angle closure during gonioscopy. Other factors include the patient's body position or aqueous flow rate. Because of the potential variability in the angle appearance, more than one gonoscopic examination is often necessary to determine a patient's risk of developing angle closure.

DYNAMIC GONIOSCOPY

With all indirect gonoscopy lenses, the mirror height and position with respect to the corneal apex will determine the view into the angle.^{4,18} A mirror closer to the center of the cornea or higher off the corneal surface will provide a

better view over a very convex peripheral iris. The Zeiss- and Posner-style lenses are well adapted to take advantage of these effects.

Tilting or sliding the lens toward the angle being viewed, or having the patient look toward the mirror being used, will allow the examiner to see over a steep, convex, peripheral iris^{18a} (Fig. 5-4A,B). It is important to perform these maneuvers when there is a break in the slit beam of light at the junction of the iris and the angle, indicating that the viewer is not seeing into the angle recess. If the viewer sees over the peripheral iris into the angle recess, the line of light on the iris should be continuous with the line of light in the angle.

These maneuvers must be performed with care, to avoid inadvertently pressing on the cornea, which can open the angle. Conversely, the angle can be closed by indentation of the peripheral cornea on the side being viewed by a Zeiss-type lens¹⁹ or compression of the sclera

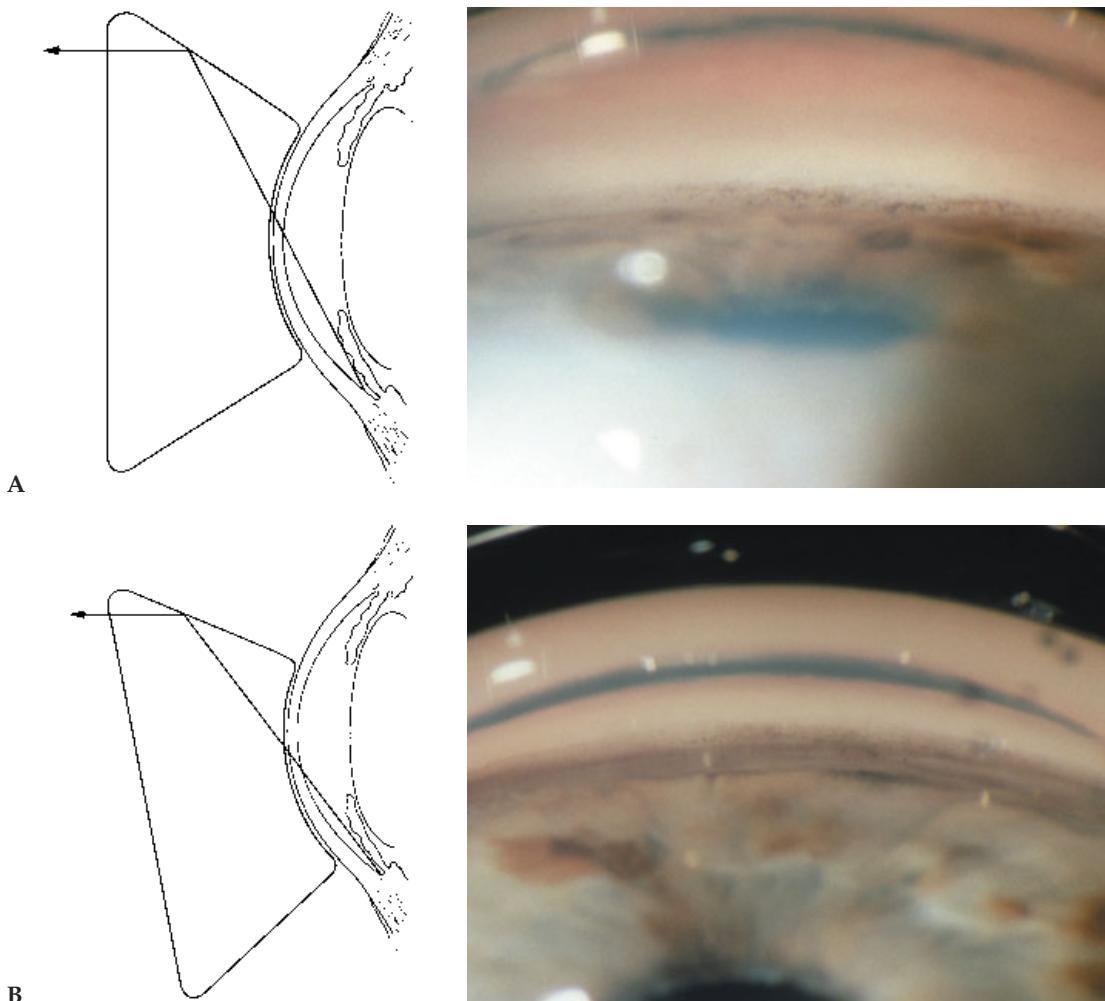


FIGURE 5-4 Lens tilting or sliding maneuver to see over a peripheral convex iris. (A) When lens and eye are in normal position, a convex iris interferes with the view into the angle, and the examiner can see only some of the anterior trabecular meshwork. (B) Tilting the lens toward the angle being viewed and/or asking the patient to look toward the mirror dramatically improves the view of the entire meshwork and scleral spur. Sliding the lens slightly toward the angle being viewed, without pressing on the eye, will have the same effect.

by a Goldmann-type lens. Tilting the lens can also result in astigmatic distortion of the light path and can shorten the trabecular meshwork.

INDENTATION GONIOSCOPY

This technique helps the examiner distinguish between synechial and appositional angle closure. Here, the lens is deliberately pushed against the central cornea. This displaces aqueous to the peripheral anterior chamber and pushes the iris and lens posteriorly.¹⁹ Sliding the lens slightly toward the angle being viewed often helps reduce corneal folds and improves the view (Fig. 5-5).

Corneal indentation will open an angle closed by apposition but fails to open one closed with permanent adhesions or peripheral anterior synechiae (PAS).^{8,19,20} Although indentation does not open an angle with synechial angle closure, the iris will still be pushed backward. This causes the iris to bow posteriorly from its anterior attachment at the PAS.¹⁹ The one circumstance in which appositional closure can be mistaken for synechial closure is when the intraocular pressure (IOP) is so high (usually greater than 40 mm Hg²⁰) that the examiner cannot exert enough force on the cornea to open the angle. In this case, the angle cannot be opened, and neither angle structures nor PAS can be seen. Corneal indentation is also useful to look for iridodialysis or a cyclodialysis cleft in an individual with a shallow anterior chamber from hypotony related to trauma.²⁰

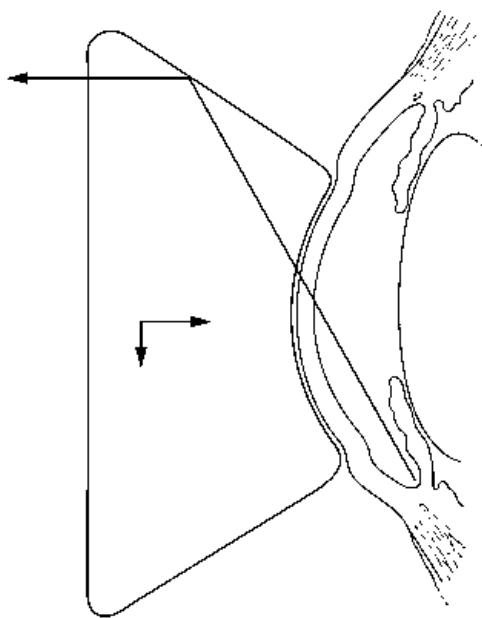


FIGURE 5-5 Indentation gonioscopy. Pressing against the central cornea (arrow to right) forces aqueous humor into the periphery of the anterior chamber, which pushes the iris and lens posteriorly. This will allow the examiner to see the anterior chamber angle structures, unless peripheral anterior synechiae are present. Sliding the lens slightly toward the angle being viewed, as well as pressing posteriorly, (arrow downward) will often improve the view.

When the angle is closed up to Schwalbe's line, the base of the corneal light wedge meets a single slit beam on the iris surface. If it is closed anterior to Schwalbe's line, the inner corneal and iris surface slit beam lines meet, but the inner and outer corneal lines of the parallelepiped do not converge. If the angle is open and all visible angle structures are seen, the examiner should see a solid line of light extending from Schwalbe's from the inner cornea, across the angle, and onto the iris.

ANGLE GRADING SYSTEMS

In general, descriptive and diagrammatic notation of all the angle findings, including changes in the angle appearance with indentation, mirror tilting, and pupil dilation or constriction, will provide sufficient information to characterize the type of glaucoma. This detailed documentation of the angle findings may be preferable to the alternative of noting an angle grade.³ Nonetheless, many examiners use some method of grading the angle, and it is important to be aware of the three common grading systems (Table 5-2).

Scheie's angle grading scheme describes the visible angle structures as ranging from "wide open" to "grade IV," or closed. Scheie emphasized that gonioscopic angle closure was not equivalent to functional closure.²¹ His system could distinguish between narrow and wide angles but not narrow and closed angles.²²

Shaffer described the angle approach and probability of closure with arabic numerals, with grade 0 as zero degrees, or closed, and grade 4 being 45 degrees, or wide open.^{5,23} Angles of 20 to 45 degrees were considered "wide open," whereas angles smaller than 20 degrees were noted to have increasing relative pupillary block and danger of angle closure.¹⁶ A slit angle is one where the angle approach is so narrow that the ciliary body and scleral spur are not visible and one cannot be certain the entire posterior trabecular meshwork (TM) is unobstructed. This angle is potentially occludable. Shaffer's grading system is used most commonly today,¹⁵ although often with roman rather than arabic numerals to document the angle degrees.^{2,20,24,26}

Spaeth's system of descriptive grading included three components: (1) angular width of angle recess, (2) configuration of the peripheral iris, and (3) insertion site of the iris root. The width of the angle recess was graded from 10 to 40 degrees. Spaeth described the lines composing this angle as one tangential to the corneal endothelial surface and another to the iris surface at Schwalbe's line.²⁷ The peripheral iris configuration was described as "s" for steep (as in plateau iris configuration), "r" for flat or smoothly convex, and "q" for concave (as may occur in pigment dispersion syndrome).^{22,27}

The insertion of the iris root was described by the anterior point of contact of the iris with the inner surface of the angle or cornea. These ranged from "A," at

TABLE 5-2 ANGLE GRADING SYSTEMS

Scheie			
Classification	Description	Findings	
Wide open	Wide open	See ciliary body band over iris root	
Grade I	Slightly narrowed	See scleral spur	
Grade II	Apex not visible	See mid scleral spur	
Grade III	Posterior half of trabecular meshwork not visible	See anterior trabecular meshwork	
Grade IV	None of angle visible	See Schwalbe's line	

Shaffer			
Classification	Angle Width	Angle Grade	Clinical Interpretation
Grade 4	35–45 degrees	Wide open	Angle closure impossible
Grade 3	20–35 degrees	Wide open	Angle closure impossible
Grade 2	20 degrees	Narrow angle	Angle closure possible
Grade 1	≤10 degrees	Narrow angle, extreme	Angle closure probable
Slit	Critically narrow angle, possibly against trabecular meshwork	Narrow angle, slit	Angle closure probable
Grade 0	0 degrees	Partial or complete closure	Partial or total angle closure

Spaeth		
Feature	Classification	Description
Width of angle recess	0, 10, 20, 30, and 40 degrees	
Peripheral iris configuration	s = steep r = regular q = queer	Sudden, sharp convex curve Relatively flat iris Concave iris
Apparent iris root insertion site	A = anterior B = behind C = C in sclera D = deep angle recess E = extremely deep recess	At or near Schwalbe's line Within trabecular meshwork At scleral spur Anterior ciliary body visible Unusual amount (>1 mm) of ciliary body band seen
12 o'clock pigmentation	0 1+ 2+ 3+ 4+	None Just visible Mild Marked Intense (black pigmented meshwork)

Schwalbe's line, to "E," for an extremely deep recess, beyond the normal amount of visible ciliary body. When the iris was appositional with the angle, the apparent iris insertion, seen without indentational gonioscopy, was noted as a letter placed in parentheses. The "actual" iris insertion site, seen with indentation, was noted with a letter not placed in parentheses. Posterior TM pigment, graded at 12 o'clock from 0 to 4+ (intense), was part of

his classification scheme. Inferior angle pigment was considered nonspecific. Spaeth also recommended the description of peripheral adhesions, blood in the angle recess or Schlemm's canal, abnormal or prominent blood vessels, angle cleavage, particles, and atrophic changes. In this system,¹⁷ the normal angle has a width of 30 to 40 degrees, an iris configuration of "r" and an iris insertion into the ciliary body band.

SYSTEMATIC GONIOSCOPY

Gonioscopy should be performed in a systematic manner, usually after tonometry. After instilling a second drop of topical anesthetic, the lens can be easily applied with the following sequence of maneuvers:

1. Hold the lower eyelid with the eye in primary gaze.
2. Grasp the upper eyelid while the patient looks down.
3. Hold the lid open while the patient looks up.
4. Place the lens on the patient's eye as it returns to primary gaze.

The patient then should fixate on a distant object to hold the eye in forward gaze and to relax accommodation. Using the slit lamp fixation target may induce unwanted accommodation.

Topical glycerin solution can temporarily improve the view through a cornea with epithelial edema caused by elevated IOP. Additional topical anesthetic drops should be instilled first to diminish the stinging that glycerin can cause.²³ The glycerin can be placed directly on the cornea or substituted for methylcellulose between the lens and cornea (Merin LM. Personal Communication. Vanderbilt University).

During gonioscopy, the examiner should note the appearance of several components of the anterior segment. These are outlined in Table 5-3 and discussed below. Iris configuration, the most posterior angle structure seen, apparent iris insertion, and angle recess angular width all can vary with changing sympathetic and parasympathetic tone,²⁸ corneal indentation, and dilation or cycloplegia.

Findings will usually vary from one quadrant to another, so they should be documented for each quadrant. This can be done either by a written description, or graphically using a drawing or diagram^{5,7,23} (Fig. 5-6). Although evaluation and documentation of all these factors may seem overwhelming at first, with repeated practice many of these components will be noted simultaneously, and the system becomes second nature.

TABLE 5-3 SYSTEMATIC GONIOSCOPY EXAMINATION

Pupil margin, iris and lens surfaces, zonules, and ciliary processes
Iris configuration
Anterior chamber angle structures
Iris insertion site
Width of the angle recess
Angle pigment
Iris processes
Iris and angle vessels
Angle abnormalities
Angle appearance after pharmacological pupillary dilation

PUPILLARY MARGIN, ANTERIOR AND POSTERIOR IRIS SURFACES, LENS SURFACES AND ZONULES, AND CILIARY PROCESSES

Slit lamp examination will usually reveal important findings on the pupillary margin and the iris surface. They can be reevaluated, however, while performing gonioscopy. Abnormalities of the posterior iris surface should be examined before the pupil is dilated, whereas the peripheral crystalline lens and zonules are more easily visualized after the pupil is dilated. In some cases, a cyst, tumor, or dislocated lens may hold the iris forward and allow inspection of the ciliary processes.⁸

Sphincter tears at the pupillary margin may indicate previous blunt trauma, whereas a space between the iris and lens in an area of iris atrophy suggests past acute angle-closure glaucoma or Herpes-related uveitis. The presence of ectropion uveae with PAS in the same quadrant may indicate a progressive anterior iris contraction, as seen in iridocorneal endothelial syndrome (ICE) or neovascular glaucoma (NVG).⁸ Pseudoexfoliative material may be visible on the pupillary margin, lens surface, posterior iris surface, or zonules. Pigment may be deposited on the lens at the base of the zonules in pigment dispersion syndrome. Vitreous seen in the space between the lens and iris suggests zonular damage from trauma or surgery, or zonular incompetence from pseudoexfoliation, homocystinuria, or other disorders.

CENTRAL AND PERIPHERAL IRIS CONFIGURATION

The iris configuration should be judged centrally and peripherally, without and then with corneal indentation. The peripheral iris configuration may provide important clues to the presence of pigment dispersion syndrome, plateau iris, or pupillary block.

If appositional angle closure is present, indentation gonioscopy may differentiate relative pupillary block from plateau iris. In relative pupillary block the convex iris indents smoothly. In plateau iris, the iris assumes a "sine wave" configuration, with the iris indenting maximally at the lens equator and then elevating peripherally over the anteriorly located ciliary processes²⁹ (Fig. 5-7A,B). One cannot be certain, however, that plateau iris is the cause for appositional angle closure until the possibility of relative pupillary block is eliminated by a patent laser iridotomy.

PEARL... During corneal indentation, the iris configuration can have either a smooth contour in relative pupillary block, or a sine wave shape in plateau iris.

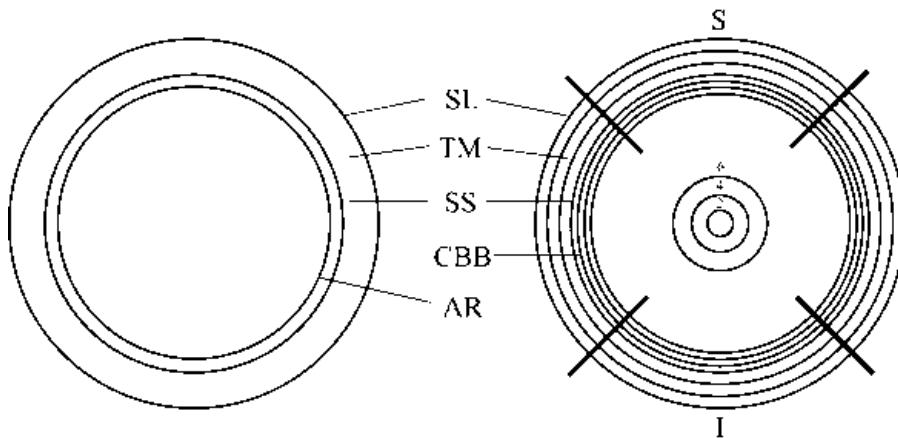


FIGURE 5-6 Diagrams for documenting gonioscopic findings. Shaffer's circular diagram (left) uses concentric circles to indicate Schwalbe's line (SL), trabecular meshwork (TM), scleral spur (SS), and the angle recess (AR). Becker's goniogram (right) indicates the view through the superior (S) and inferior (I) mirrors, the position of Schwalbe's line (SL), trabecular meshwork (TM), scleral spur (SS), and the iris insertion site in the ciliary body band (CBB). Pupil size in millimeters is indicated in the center of the diagram.

ANTERIOR CHAMBER ANGLE STRUCTURES

Pigment on Schwalbe's line can be confused with TM that is pigmented, resulting in a closed angle being described as open (see Chapter 16, Fig. 16–5). This is especially likely to occur if circumferential, synechial angle closure to the mid or anterior TM creates a relatively flat iris and wide angle approach. In that case, nonpigmented TM may be confused with scleral spur, and pigmented Schwalbe's line with posterior TM.³⁰ This confusion can be avoided by using the corneal parallelepiped to identify Schwalbe's line, and indentation to demonstrate the PAS.

In the normal young adult the ciliary body band will be the most posterior visible portion of the angle. It can

vary in color from gray in a blue-eyed individual to brown in a dark-eyed person. It will not be seen in infants or young children because the angle recess does not completely form until approximately 5 years of age.³¹ If the ciliary body band appears unusually wide, if pale tissue is seen posterior to the ciliary body band, or if the apparent width of the ciliary body band varies widely in different quadrants, then the clinician should consider the possibility of angle recession. Careful comparison of the two eyes can help distinguish a wide ciliary body band from circumferential or localized angle recession.

If appositional angle closure or a potentially occludable angle is found, with or without synechiae, the clinician should reassess the angle appearance after creating a patent

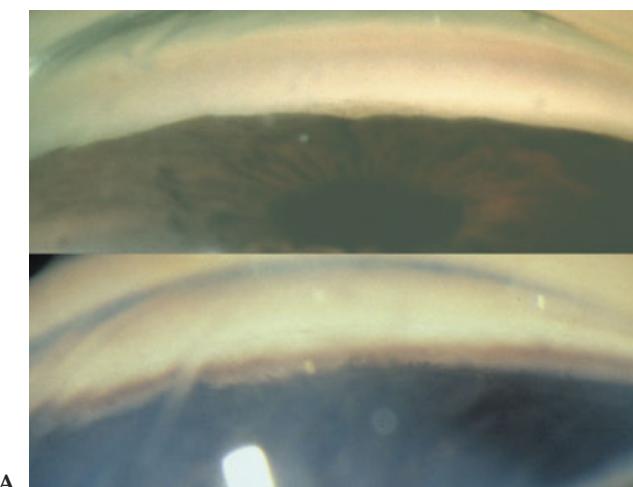
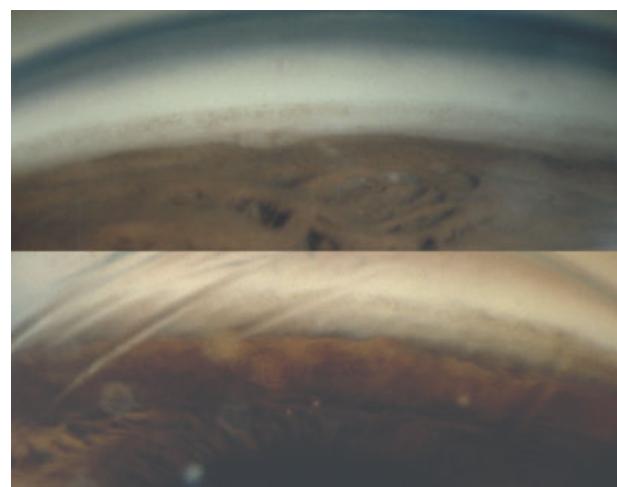


FIGURE 5-7 Iris configuration during indentation gonioscopy for appositional closure in relative pupillary block and plateau iris. (A) An eye with appositional angle closure due to relative pupillary block before (above) and during (below) indentation gonioscopy. Note smooth indentation of iris. (B) An eye with plateau iris before indentation gonioscopy (above), showing only some of the trabecular meshwork, with a small amount of scleral spur. During indentation gonioscopy (below) the iris is pushed toward the lens equator, but remains elevated peripherally by the anteriorly located ciliary processes. This is the "sine wave" sign.



B

TABLE 5-4 IRIS INSERTION SITES IN THE ADULT

Iris Insertion Site	Diagnosis(es)
Cornea	Iridocorneal endothelial syndrome (ICE), posterior polymorphous dystrophy, neovascular glaucoma (NVG), previous postoperative flat chamber, iris in limbal or scleral wound
Schwalbe's line	Angle closure
Trabecular meshwork	Congenital glaucoma
Anterior trabecular meshwork	Angle closure
Pigmented trabecular meshwork	Angle closure or trabeculogoniodysgenesis
Scleral spur	Hyperopia, narrow angle or plateau iris, early creeping angle closure, or trabeculogoniodysgenesis
Ciliary body band	Normal, emmetropia, or myopia
Beyond ciliary body band, with or without scarring to higher (more anterior) levels	Angle recession
Iris root detached in one region	Iridodialysis
Ciliary muscle detached from scleral spur	Cyclodialysis
Variable insertion site	Peripheral anterior synechiae (PAS) or angle recession

laser iridotomies and eliminating relative pupillary block. Gonioscopy should be repeated in each eye individually, before and after pupil dilation with phenylephrine.

IRIS INSERTION SITE

The iris insertion site should always be determined. Spaeth has defined the "apparent" iris insertion site as that seen without indentation gonioscopy and the "real" iris insertion site as that seen during indentation.²⁷ It may be impossible, however, to ascertain the "real" iris insertion site if compression is ineffective because of high IOP.

In infants and young children, prior to the formation of the angle recess, the iris inserts into the scleral spur or posterior TM. In congenital glaucoma the iris inserts anteriorly and the scleral spur may be absent or underdeveloped, with the ciliary muscle inserting into the TM.^{31,32} In the normal adult the iris inserts into the ciliary body band,³³ which is wider in myopia and narrower in hyperopia.³ In hyperopes or individuals with a narrow angle or plateau iris, the iris root often inserts into scleral spur.⁶ Irregularities in the insertion site in the adult may be a normal variant or may be caused by Axenfeld-Rieger syndrome, angle recession, a cyclodialysis cleft, or localized PAS. The insertion site may be covered or traversed by iris processes. Table 5-4 lists normal and abnormal iris insertion sites, along with their clinical implications.

WIDTH OF THE ANGLE RECESS

The examiner should always estimate the angle of approach into the anterior chamber angle recess. This angle is created by one line tangential to the inner surface of the posterior TM and another tangential to the anterior surface of the peripheral iris. The peripheral iris is

used because the iris configuration can vary widely from the central to the peripheral regions.²²

The angle recess width can be graded from 0 to 45 degrees and it will vary with changes in iris convexity and with the length and thickness of the iris root.³⁰ It may be irregularly narrow because of lens dislocation or subluxation, or iris or ciliary body cysts or tumors, and irregularly wide because of lens dislocation.⁸ The width of the angle recess depends on the position and thickness of the lens, ciliary body thickness, and pupil size, each of which may be influenced by specific factors outlined in Table 5-5.

TABLE 5-5 FACTORS THAT AFFECT ANTERIOR CHAMBER ANGLE RECESS ANGULAR WIDTH

Factor	Condition
Iris insertion site	
Iris thickness and rigidity	
Lens thickness	Age Medications Blood sugar
Lens position	Medications Accommodative state Changes in ciliary body
Ciliary body thickness	Inflammation Effusion Congestion
Pupil size	Light Accommodation Medications Sympathetic and parasympathetic tone

In general, the superior and nasal angles tend to be narrower than the inferior and temporal angles.¹⁵ The superior angle may appear narrow during indirect gonioscopy because the upper pole of the crystalline lens moves slightly forward when the patient is sitting upright.²³ The narrower appearance also may result from pressure on the superior angle by the upper lid and the edge of a Goldmann or Koeppe lens along with the Bell's phenomenon.³⁴ Ultrasound biomicroscopy studies have found that angle width does not vary between quadrants in the supine patient.³⁴

A break or parallactic shift in the line of light traversing the angle and iris surfaces may indicate that the examiner does not have an adequate view into the angle recess over a convex peripheral iris.^{15,30,35,36} This suggests that the angle may be dangerously narrow.³⁶

ANGLE PIGMENT

In a normal infant or child there is no pigment in the angle. Schwalbe's line, the anterior TM, and scleral spur are white or translucent, and the posterior TM is grayish. After the angle recess has formed, the ciliary body band appears gray to brown.

In the normal adult, angle pigmentation is most prominent inferiorly and nasally,^{8,38} whereas temporal pigment is less common. The ciliary body and posterior TM are generally more pigmented than Schwalbe's line. Pigmentation is usually most dense in the posterior TM because the pigment is filtered out of the aqueous prior to its exit into the canal of Schlemm. Pigmentation of Schwalbe's line, although unusual, can occur inferiorly as particulate matter and cells collect on the ledge formed at the base of the corneal endothelium by the difference in the curvature of the cornea and sclera.^{18a}

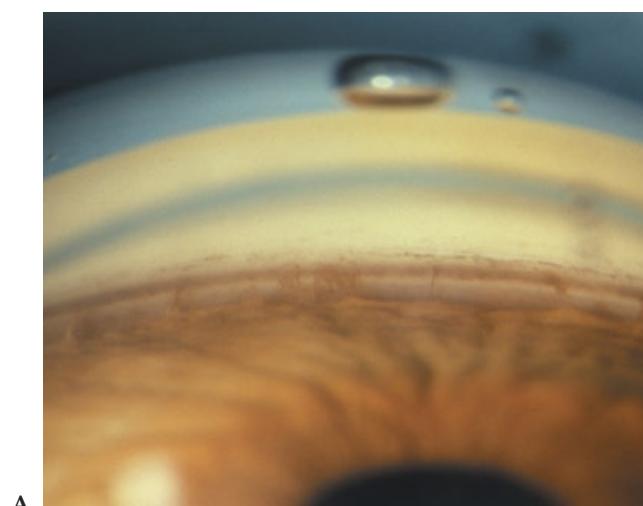
In pseudoexfoliation syndrome, a wavy line of speckled pigment irregularly scattered over the inner portion of the peripheral cornea, called Sampaolesi's line, can result from adherence of pigment to pseudoexfoliative material.³⁹ Pigment deposition on Schwalbe's line and the corneal endothelium anterior to Schwalbe's line also can occur with intermittent angle closure and iris apposition to these structures.^{13,37,40,41}

Increased angle pigmentation can occur as a normal variant, or in eyes with pigment dispersion syndrome, pseudoexfoliation, diabetes mellitus, oculodermal melanocytosis,¹⁴ pigmented tumors, iris-lens chafing from posterior chamber intraocular lenses,²⁰ previous trauma,³⁷ hemorrhage or inflammation, or after laser treatment or incisional surgery. In pigment dispersion syndrome, pigment is confluent in the posterior, inner TM. In pseudoexfoliation, the pigment appears granular and speckled across the uveoscleral meshwork and elsewhere. Pigment in the angle must be distinguished from pigmented uveal meshwork, a normal variant seen in eyes with dark irides, and from invasion by a pigmented tumor.

IRIS PROCESSES

Normal iris processes are fine, threadlike, or slightly wider strands of iris tissue crossing from the iris base over the angle recess to the scleral spur or the posterior TM (Fig. 5-8A). They are seen most commonly in the nasal, followed by the inferior, quadrant.³⁷ Abnormal iris processes in Axenfeld-Rieger syndrome extend from the iris base to a prominent, anteriorly located Schwalbe's line. They often are thicker and wider than normal iris processes.

Iris processes should be distinguished from pigmented uveal meshwork tissue, which appears as a fine mesh lining the angle structures from the ciliary body to the scleral spur or TM. This tissue is generally nonpigmented, fine, and lacy in youth, and pigmented and thicker with porous openings in adulthood.⁸ Iris processes differ from PAS in that the latter are tentlike or medium- to broad-based iris adhesions to any level of the angle.



A



B

FIGURE 5-8 Normal gonioscopic findings. (A) Iris processes. (B) Circumferential vessel over the ciliary body in a patient with blue irides.

IRIS AND ANGLE VESSELS

Vessels on the surface or at the base of the iris usually are not seen in eyes with dark brown irides because they are hidden within the thick stroma. In contrast, angle vessels are seen in approximately 50% of normal eyes with blue irides, and in 16% of eyes with lighter brown irides, which have an intermediate stromal thickness. Radial iris and circular ciliary vessels are seen more often (71% and 66%) than radial ciliary vessels (43%), and much more often than circular iris vessels (14%).

Normal iris vessels tend to emerge from the iris stroma or the ciliary body (Fig. 5–8B). They are also relatively large and have a radial or circular orientation. In contrast, abnormal, new iris vessels in ocular ischemic or inflammatory conditions are finer, lacier, more tortuous, and more randomly oriented.^{8,36,39,40}

It is extremely rare to see vessels in or on the angle structures in a normal eye, except at the iris base or overlying the ciliary body. Angle neovascularization can be seen within the TM or crossing from the iris base to the scleral spur and TM. These abnormal vessels can be extremely fine, resembling a faint reddish hue in the meshwork, or can be a vascular or fibrovascular plexus with or without overlying red blood cells. In advanced cases, contracture of the fibrovascular membrane will produce partial or complete PAS.

The vessels that can occur in Fuchs' iridocyclitis tend to be fine and have a wandering course in the angle. They bleed easily when the IOP is lowered during surgery. Their associated membrane does not tend to cause PAS.⁸

Infants with congenital glaucoma may have vessels on the iris surface because of incomplete regression of the tunica vasculosa lentis. These vessels are usually associated with an incompletely developed iris stroma and may be engorged prior to treatment of the elevated IOP. When seen in the angle, they tend to loop in and out of the iris. They may disappear as the infant ages.

ANGLE ABNORMALITIES

Peripheral Anterior Synechiae

Medium- to broad-based PAS can occur in angle closure from pupillary block and plateau iris. They can be tent-like and generally inferior in inflammatory diseases, possibly because of iris adhesion to points of inflammatory precipitates.²⁰ PAS with small points of adhesion can also occur following argon laser trabeculoplasty if the laser is applied too far posteriorly, or even if the laser is applied in the correct location in an eye with a peripherally convex iris. In creeping angle closure, the PAS usually are broad, mimicking a progressively more anterior iris insertion site.³⁰ They can be adherent to any level of the angle up to Schwalbe's line, but usually not to the cornea. High PAS to the cornea are more likely to occur in iridocorneal

endothelial syndromes, posterior polymorphous dystrophy, neovascular glaucoma, nanophthalmos, previous postoperative anterior chamber shallowing, or incarceration of iris in a limbal or scleral wound.

Blood in Schlemm's Canal

Blood in Schlemm's canal can indicate ocular hypotony, elevated episcleral venous pressure, iridocyclitis,³⁷ or compression of the episcleral vessels in a normal eye by a large-diameter gonioscopy lens. This finding must be distinguished from the faint flush seen with early neovascularization of the TM. If blood is seen in Schlemm's canal during Koeppe gonioscopy, the examiner should always consider the possibility that this may be artifactual because placing the patient in the supine position can temporarily increase episcleral venous pressure.⁶

Cellular or Particulate Matter Deposits

Inflammatory precipitates may be present on Schwalbe's line or the TM even when no significant anterior chamber reaction is seen. White, red, or ghost blood cells may be layered inferiorly or may cover the posterior TM throughout the angle circumference. Pseudoexfoliative material sometimes can be seen on Schwalbe's line or in the angle recess.

Tumors or Membranes

Tumors can extend from the iris surface across the angle or invade from the ciliary body into the angle. The angle should be studied for transparent or slightly opaque stromal, endothelial, or epithelial membranes lining the surface of the corneal endothelium, angle structures, and iris. In eyes that have undergone surgery and have a history of episodes of blurred vision, the wound should be evaluated for a fibrovascular membrane or vessels within the wound from which bleeding could occur.

Foreign Body or Other Material

Materials heavier than aqueous usually will be found in the inferior angle. The cornea may be edematous above the location of the foreign body.¹⁴ Materials lighter than aqueous (silicone oil, perfluorocarbon gas, or air) will be located in the superior angle.

Glaucoma Filtering Surgery Sites or Drainage Implant Tubes

In eyes with a history of filtering surgery, gonioscopy allows the surgeon to evaluate the patency of the internal ostium and the view through the ostium into the sub-Tenon's or subconjunctival space. Fibrin, blood, iris, or vitreous can be seen in the ostium in the early postoperative period. Closure of the internal ostium, or, more commonly, a patent internal ostium with closure of the scleral flap, may occur later in the postoperative phase. PAS may form on either or both sides of the ostium. Iris tissue may adhere to

the cornea anterior to the ostium and can either allow flow around the sides of the adhesion or block flow completely if synechiae surround the entire ostium.

The position and patency of glaucoma drainage device tubes located in the angle of a phakic eye or the posterior chamber of an aphakic or pseudophakic, vitrectomized eye should be examined. Fibrin, blood, vitreous, or iris may be present at the tip or in the lumen of the tube. The tube may be surrounded or covered by a fibrous, fibrovascular, or epithelial membrane or PAS in eyes with a history of neovascular glaucoma, iridocorneal endothelial syndrome, or epithelial downgrowth.

RE-EVALUATION OF ANGLE APPEARANCE AFTER PHARMACOLOGICAL PUPILLARY DILATION

Gonioscopy should always be repeated in eyes with suspicious, but not occludable, angles after pupillary dilation with short-acting cycloplegic and mydriatic agents such as tropicamide and phenylephrine. It is important to remember, however, that the angle appearance following pharmacological dilation may differ from that produced by physiological dilation. Similarly, the appearance with a mid-dilated pupil may differ from that of an eye with a fully dilated pupil. Dilation with a cycloplegic agent can make the angle appear more open, because of relaxation of the ciliary muscle and posterior movement of the iris-lens diaphragm. The angle may appear narrower or closed following mydriatic dilation, due to bunching of the iris into the angle, or it may appear more open because of relief of pupillary block.

Elevated IOP after pharmacologic dilation does not necessarily mean that the angle has closed. It instead can reflect poor baseline aqueous outflow (especially in eyes that depend on miotic agents for pressure control) or outflow blockage by pigment or pseudoexfoliative material released following pupillary dilation.^{42,43}

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INTRAOCULAR PRESSURE AND TONOMETRY

Henry Jampel, M.D.

The measurement of intraocular pressure (IOP) is an essential part of the ocular examination. First associated with glaucoma by von Graefe,¹ elevated IOP can produce glaucomatous optic nerve damage in animals² and remains the most important risk factor for glaucoma in humans.^{3,4} Lowering IOP is currently the only widely accepted method of preventing glaucomatous optic nerve damage or retarding its progression once present.

In order to use IOP measurements to care for individual glaucoma patients, one must understand (1) the distribution of IOP in the normal and glaucomatous populations of different racial origins, (2) the factors that influence IOP, (3) how IOP can fluctuate, and (4) factors that can influence the measurement of IOP. This chapter focuses on these four points. Another important consideration, the effect of IOP on the presence of glaucomatous optic neuropathy, is discussed in Chapters 1 and 15.

DISTRIBUTION OF INTRAOCULAR PRESSURE

IOP has been measured in several population-based studies^{5–14} (see Chapter 1, Table 1–2). Unfortunately, these studies cannot be compared directly, due to differences in study populations, methods of measuring IOP, and inclusion or exclusion of eyes with glaucoma, as defined by optic disc or visual field changes. Nonetheless, two observations are apparent: (1) mean IOP varies substantially among these studies, possibly due to racial differences; and (2) normal IOP appears to have an approximately normal distribution, with several studies finding a skew, or tail, toward higher pressures. How much of this tail represents undetected glaucoma patients is unclear.

FACTORS THAT INFLUENCE INTRAOCULAR PRESSURE

AGE AND GENDER

Several studies provide information about gender and age.^{5,7–10,12,14} Most of these studies find slightly higher pressures in women. Although IOP generally increases slightly with age, one study, from Japan, notes a decrease in IOP with age⁵; another, the Barbados Eye Study, based on subjects of African descent, observed a much larger increase with age.¹⁴

BLOOD PRESSURE

Several studies suggest that, in subjects without glaucoma, IOP can vary with blood pressure. Although IOP may be associated with systolic, but not diastolic, blood pressure in Barbados,¹⁵ other surveys found a positive association with both systolic and diastolic blood pressure.^{9,16} In the Baltimore Eye Survey¹⁷ a 10 mm Hg increase in either systolic or diastolic blood pressure was identified with a 0.25 mm Hg or 0.19 mm Hg rise in IOP, respectively ($p < 0.001$). On the other hand, the association of increased blood pressure with chronic open-angle glaucoma is less clear, in spite of its relationship to IOP in normal individuals.^{15,16}

DIABETES MELLITUS

Most recent studies^{9,15,18,19} suggest an association between diabetes mellitus and IOP. As with blood pressure, some investigators,^{19,20} though not all,^{15,16} associate diabetes with chronic open-angle glaucoma. Regression analyses show that blood pressure and diabetes together account for less than 10% of the variability in IOP.^{9,15} This is fully discussed in Chapter 1.

CONTROVERSY

Although relationships between intraocular pressure and diabetes mellitus and systemic hypertension have been consistently demonstrated, the relationship of these factors to glaucomatous optic nerve damage remains controversial.

OTHER SYSTEMIC ASSOCIATIONS

Both black¹⁵ and white populations⁹ demonstrate a positive association of IOP with body mass index and pulse rate. In addition, Shiose et al. have suggested that IOP may also be related to obesity.²¹ Other, less consistent, associations have also been reported.

ANESTHETICS

There are two reasons for understanding how systemic anesthetic agents can influence IOP. First, lower IOPs are generally safer during intraocular surgery, particularly for repair of traumatic corneal and scleral lacerations. Second, when measuring IOP under general anesthesia for diagnosis or therapy, recognizing how the anesthetic affects IOP can help the practitioner better estimate the "true" awake pressure.

Most anesthetic agents lower the IOP and are suitable for general anesthesia on an open globe. Premedications, such as diazepam and midazolam given intravenously, decrease IOP, as do intramuscular morphine and Innovar.²² The inhalation anesthetics halothane,²³ enflurane,²⁴ and isoflurane all reduce IOP by approximately 20 to 40%.²² A normal IOP measurement obtained during halothane anesthesia does not preclude the presence of glaucoma, and an elevated IOP with this and all general anesthetics should prompt a careful examination for optic nerve damage and other signs of glaucoma.²⁵

Unfortunately, succinylcholine, necessary for muscular paralysis, can increase IOP, in part by stimulating contraction of the extraocular muscles. Several pretreatments have attempted to abrogate this effect, but without success. Succinylcholine, laryngoscopy, and endotracheal intubation^{22,26} all tend to negate the beneficial effect of anesthetic agents upon IOP during surgery.

Because most anesthetics tend to lower IOP, tonometry under general anesthesia, as required for diagnosis and treatment of children with infantile or childhood glaucoma, generally provides an underestimation of the awake IOP. In contrast, intramuscular ketamine does not appear to lower the IOP and may in some instances raise it. IOP in children appears to be higher with ketamine than with halothane.²⁷ Using a MacKay-Marg electronic applanation tonometer in 10 healthy children, Ausinsch-

et al. concluded that ketamine had no effect on IOP.²⁸ Although one study reported a transient decrease in pressure,²³ others have found a mean increase of 2 mm Hg,²⁹ and another a marked increase following administration of ketamine.³⁰

Extrapolating the awake IOP from IOP measurements made under anesthesia remains challenging, and is one of the reasons that decisions about glaucoma control in children must incorporate information in addition to the IOP, such as the optic nerve appearance and corneal diameter.

PITFALL... Almost all anesthetics, but particularly inhalation anesthetics, lower IOP. One can mistakenly interpret an IOP measured under anesthesia as "normal" when the actual IOP is higher. Ketamine used as an anesthetic does not lower IOP and therefore minimizes this problem.

EXERCISE

In young subjects without glaucoma, physical exertion acutely decreases IOP.³¹⁻³⁵ In general, the greater the exercise, the greater the effect.^{34,36,37} In Scandinavia, one episode of intensive exercise produced the greatest pressure lowering in subjects with elevated IOP, but it had a less consistent effect on treated glaucoma patients.³³ In another study, the IOP in seven glaucoma patients fell by a mean of 12 mm Hg after running.³⁶

The effects of chronic exercise training upon IOP have greater implications for the prevention and treatment of glaucoma. An early study randomized subjects to either participate or not participate in a 6-month exercise program and found that IOP fell to a similar extent in both the experimental and the control groups.³⁸ However, Passo subsequently evaluated the effect of a several-month exercise regimen upon IOP in young, sedentary patients³⁹ as well as in a small group of glaucoma patients with elevated IOP but no optic nerve damage.⁴⁰ Passo found that IOP was over 4 mm Hg lower after exercise training than before, and that IOP returned to the pre-exercise level within 3 weeks of stopping the exercise.⁴⁰ Qureshi determined that a 3-month exercise program produced a mean lowering of IOP approximately 1 mm Hg greater than that seen in nonexercising control subjects.⁴¹

Although it would be most relevant to evaluate the effect of chronic light exercise (e.g., walking or using an exercise bicycle several times a week) in older patients with either glaucoma damage or elevated IOP, this "ideal" study has not yet been done. Nevertheless, current information indicates that exercise produces a decrease in resting IOP that is sustained as long as the exercise is performed regularly.

How exercise decreases IOP remains controversial. Ashkenazi et al. found that IOP reduction was inversely related to plasma osmolarity,³⁵ whereas Harris et al. concluded that IOP correlated best with an increase in blood lactate, but not with changes in metabolic rate or plasma osmolarity.⁴²

PEARL... When patients ask how they can change their lifestyle to help their glaucoma, they can be told “with regular exercise.”

In patients with pigment dispersion, exercise can release pigment within the eye and lead to marked increases in IOP.⁴³ Larger studies, however, do not show that exercise consistently elevates IOP,^{44,45} even in eyes with documented pigment release.⁴⁵

TONOMETRY

Repeated measurements with the Schiøtz or Goldmann tonometers can lead to lower estimations of the IOP.^{46,47} Various explanations have been offered to explain the decrease in IOP with repeated Goldmann tonometry, including fluorescein staining of the cornea⁴⁷ and an effect of the topical anesthetic.⁴⁶ One study found that repeated applanation tonometry caused a decrease in the IOP of the fellow eye.⁴⁸

FLUCTUATIONS IN INTRAOULAR PRESSURE

Fluctuations of IOP frustrate our understanding of the relationship between IOP and optic nerve damage and complicate assessment of our efforts to lower IOP. Rapid changes in IOP occur with the ocular pulse, as demonstrated by oscillations of the applanation tonometer mires and the pneumatonometer tracing. When there are large ocular pulsations, the IOP should be read as the middle of the distance over which the mires (applanation tonometer) or tracing (pneumatonometer) move. The variation in IOP, even over the course of an hour, can be dramatic.^{49,50}

Many investigators have studied circadian variations in IOP (i.e., those occurring with a frequency of approximately 24 hours). Understanding how IOP varies over the course of a day aids the interpretation of the solitary IOP measurements we make in standard clinical practice. In normal eyes, circadian variation in IOP ranges from 3.17 ± 1.2 to 6.5 ± 1.4 mm Hg^{49,51–53} whereas the mean IOP variation ranges from 4.8 ± 1.8 to as high as 18.4 ± 8.4 mm Hg in untreated glaucoma patients.⁵⁴ Zeimer has shown that the degree of variability in IOP over the day increases as the mean IOP in the eye increases.⁵⁴ In other words, the higher the IOP, the more variable it is.

PEARL... Eyes with higher mean IOPs will have greater variability in their IOP measurements.

IOP management would be simpler if all eyes had the same circadian rhythm, with the peak and minimum IOPs occurring at predictable times of the day. In general, peak IOP tends to occur in the morning, with the trough in the afternoon or evening.⁵⁴ Unfortunately, although some eyes have a “regular” rhythm, with the highest and lowest pressures occurring at approximately the same time every day,⁵¹ the timing of these peaks and troughs is highly variable (Fig. 6–1). In others, circadian rhythm is “irregular,” with peaks occurring randomly from one day to the next. Thus aggregate results cannot be applied to individual patients.

The rationale for the unilateral therapeutic trial of medication to lower IOP assumes that the circadian rhythm of a person’s two eyes will be similar, if not identical. This appears reasonable, given that Horie and Kitazawa reported differences of less than 2 mm Hg between the two eyes in 93% of normal patients and in 82% of patients with ocular hypertension.⁵⁵ In glaucoma patients with IOP below 21 mm Hg, Yamagami et al. found a close agreement between the two eyes,⁵⁶ suggesting that, for many patients, IOP between the two eyes is highly correlated.⁴⁹

Other fluctuations in IOP include a transient, marked increase in IOP associated with awakening in both normals and treated glaucoma patients,^{57,58} and seasonal variations. In Israel, IOP, measured by Schiøtz tonometry, tends to be lower in July than in November through February,⁵⁹ with similar variations seen in Wisconsin using Goldmann applanation tonometry.⁹

FACTORS THAT INFLUENCE INTRAOULAR PRESSURE MEASUREMENT

Useful measurements of IOP must be simple, repeatable, and accurate. Understanding the principles and use of the tonometer, or instrument used to measure the IOP, is crucial to obtaining measurements that accurately reflect pressure within the eye. Other factors influencing the accuracy of IOP measurements include the thickness and topography of the cornea, with which all of these instruments must interface.

TONOMETER

All tonometers work by deforming the globe and correlating this deformation with the pressure within the eye.⁴ When there were only two commonly used tonometers, the Schiøtz and the Goldmann, the former was referred to as an indentation tonometer and the latter as an

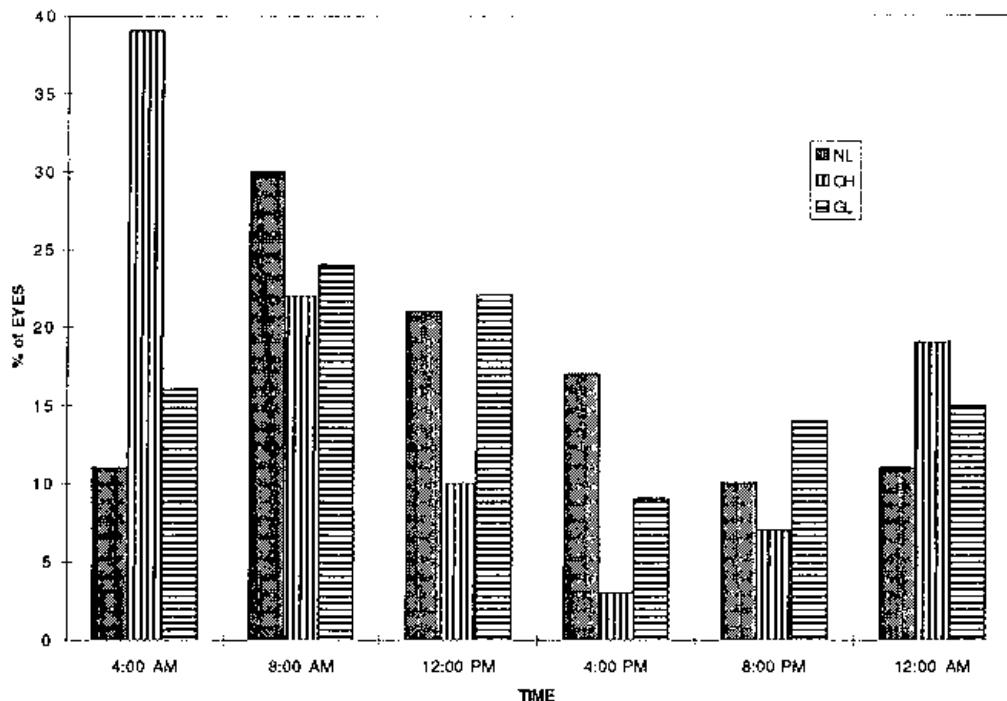


FIGURE 6-1 Summary of the time of intraocular pressure (IOP) peaks in normal eyes (NL), eyes with ocular hypertension (OH), and eyes with glaucoma (GL). Although most eyes peak in the morning, others do not. In some, peak IOP occurs randomly from day to day. (Adapted from Tables 21-2, 21-4, and 21-6 in Zeimer.⁵⁴)

applanation tonometer. In fact, these two tonometers differ only in the extent to which they indent the globe. Other tonometers, developed to achieve specific clinical goals, such as increasing portability or minimizing contact with the eye, differ only in the methods and technologies used to deform the eye. Table 6-1 compares the most commonly used instruments with regard to accuracy, portability, and ease of use.

GOLDMANN TONOMETER

The Goldmann applanation tonometer represents the gold standard for IOP measurement and is used in all the major randomized glaucoma clinical trials. Here, the force required to flatten, or applanate, a constant area of the cornea is measured and related to the IOP using the Imbert-Fick law. This law describes the relationship

between the pressure within a sphere and the force required to flatten a portion of that sphere (pressure = force/area flattened) for a perfectly spherical, dry, and infinitely thin surface. Goldmann adapted this formula to the human cornea, which is neither infinitely thin nor dry. He determined that corneal inflexibility (requiring additional force for applanation), is equal and opposite to the attraction of the surface tension of the tear film (drawing the tonometer tip to the cornea), at diameters of applanation between 2.5 and 4 mm. The Goldmann tonometer uses an applanation diameter of 3.06 mm because the grams of force used to flatten the cornea to this extent, multiplied by 10, yields pressure in mm Hg.

The Goldmann applanation tonometer is mounted on the slit-lamp and consists of a strain gauge connected by a lever to a plastic tip (Fig. 6-2A). When the tip face contacts the cornea, a birefringent in the tip splits the view of the tear film meniscus into two semicircles. Rotating a dial attached to the gauge varies the force against the cornea and alters the alignment of the two semicircles (Fig. 6-3A,B).

Goldmann applanation tonometry is performed with the patient seated at the slit-lamp. A drop of anesthetic containing fluorescein, or proparacaine plus fluorescein applied on a paper strip, improves visibility of the tear meniscus when viewed with a bright cobalt blue light. Separating the lids gently with thumb and forefinger, the tip is moved slowly toward the cornea until it makes contact, producing two green semicircles as viewed through

TABLE 6-1 COMPARISON OF TONOMETERS

	Accuracy	Portability	Ease of Use
Goldmann	++++	+	++
Tonopen	+++	++++	++++
Pneumatonograph	++	++	+++
Schiøtz	+	++++	+

+, least favorable; +++, most favorable.



FIGURE 6-2 Some commonly used tonometers. (A) Goldmann applanation tonometer mounted on a Haag-Streit slit-lamp. (B) Hand-held applanation tonometer, which can function with the patient either supine, as shown, or sitting up. (C) The Tonopen must be held perpendicular to the cornea. (D) The covering is pulled tight enough to flatten it over the tip of the instrument. Note the radial folds in the membrane, indicating that it is not too tight. (E) Pneumatonometer. (F) Schiøtz tonometer.

the slit-lamp. Moving the slit-lamp up or down to center the prism on the cornea will equalize the semicircles, whose inner edges are then aligned by turning the tension dial. At this point, the dial indicates pressure in millimeters of mercury.

Patients who “squeeze” their eyelids against the examiner’s hold can raise their IOP and artificially raise the measurement. Making the patient comfortable in the slit-lamp, approaching the eye slowly with the tonometer,

and holding it just in front of the eye for several seconds prior to applanation can help the patient relax and reduces this source of error. In addition, an IOP reading in the first eye that is several mm Hg higher than that in the second eye measured may also indicate an anxious patient. If this occurs, the examiner should recheck the IOP in the first eye to validate the initial measurement.

The accuracy of the Goldmann applanation tonometer depends on the amount of fluorescein in the tear film,

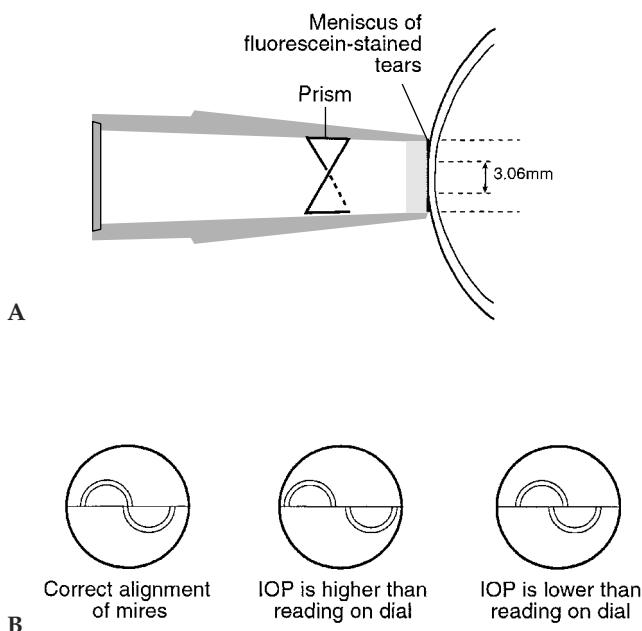


FIGURE 6-3 (A) The Goldmann applanation tonometer produces a tear film meniscus when the tip contacts the cornea. (B) The biprism splits the view of the circular meniscus into semicircles, which are aligned at their inner edges once the tip flattens a corneal area with diameter of 3.06 mm as shown in (A). (Modified from Shields MB. *Textbook of Glaucoma*. 4th ed. Baltimore, Md: Williams Wilkins; 1998:56.)

and on the thickness and curvature of the cornea. A thick, excessive tear film can produce broad mires, causing an overestimate of IOP. Blotting away excess tears and wiping the tonometer tip with a tissue usually resolve this problem. Alternatively, the Goldmann tonometer may read artificially low when applied to thin corneas, as in high myopia, and possibly in children^{60,61} because corneal

inflexibility is actually less than assumed for the normal eye. In corneas with high astigmatism, with the mires oriented horizontally, this tonometer will either underestimate or overestimate IOP by 1 mm Hg for every 4 diopters of either with-the-rule or against-the-rule astigmatism, respectively.⁶² Rotating the tonometer prisms to bring the axis of least corneal curvature opposite the red line on the prism holder,⁶³ or averaging readings taken with the mires horizontally and vertically,⁶² can minimize this error.

HAND-HELD APPLANATION TONOMETERS

These are adaptations of the Goldmann applanation tonometer, with the prisms of the tonometer counterbalanced to allow tonometry with the patient in any position (Fig. 6-2B). They are particularly useful for measuring IOP in children and bedridden patients. Accuracy in either the horizontal or vertical position is comparable to the Goldmann tonometer.⁶⁴ Current availability of these instruments is limited.

TONOPEN

The Tonopen (Fig. 6-2C,D) is a highly portable, battery-operated tonometer that uses a core sensing mechanism to measure IOP, surrounded by an annular ring, or sleeve, that absorbs the force required to bend the cornea. This principle, illustrated in Figure 6-4A,B,C, was developed initially with the MacKay-Marg tonometer, which is no longer manufactured.^{65,66}

A strain gauge connected to the core sensing mechanism in the tip of the Tonopen is activated when it touches the cornea, producing a waveform of pressure change over time. A microprocessor differentiates acceptable from unacceptable measurements, stores only the former, and averages them to give a final IOP. The variation among

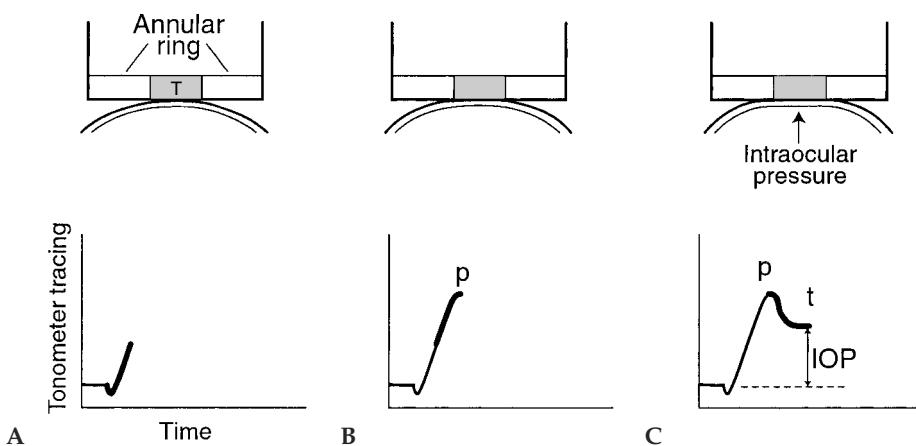


FIGURE 6-4 The principle of MacKay-Marg tonometry. (A) As the sensitive surface of the transducer (T) contacts the cornea, the tracing begins to rise. (B) The peak (p) is reached when the diameter of contact equals that of the transducer surface, causing maximal deflection of the sensor. (C) With further corneal flattening, the force of bending cornea is transferred to the surrounding sleeve, and tracing decreases to a trough (t) when the diameter of contact equals 3 mm. The distance from the baseline to the trough indicates the IOP reading. (Modified from Shields MB. *Textbook of Glaucoma*. 4th ed. Baltimore, Md: Williams Wilkins; 1998:59.)

the averaged measurements is also calculated as the ratio, in percent, of the variance to the average IOP (i.e., <5% signifies that the variance is <5% of the average IOP).

The Tonopen is the most convenient of the tonometers to use. The probe tip is covered with a sterile disposable rubber cap before use, stretched flat over the tip without excessive tension that could dampen movement of the strain gauge (Fig. 6–2D). Calibration, an internal process that requires no additional instruments, should be checked before every measurement session. After instilling a topical anesthetic, the probe tip, held perpendicular to the globe, is gently tapped against the central cornea. A high-pitched beep signals an acceptable reading. Measurements are continued, and after several additional beeps, another sound occurs, indicating that enough readings have been obtained. The instrument digitally displays the IOP and the error of its measurement.

The Tonopen accurately measures IOP in human autopsy eyes in which the pressure is manometrically controlled.⁶⁷ The correlation between the Tonopen and Goldmann tonometer is (in general) good, although the Tonopen tends to underestimate pressure at high IOP⁶⁸ and overestimate it in eyes with low pressure.^{68,69}

Accurate, repeatable measurements with the Tonopen require that the operator bring the tip into contact with the cornea using a consistent, firm motion. Excessive force can result in artificially high readings, whereas mere contact with the corneal tear film can produce low readings. Acquiring this skill requires diligent effort and practice. Simultaneous comparison with Goldmann applanation tonometry will help the beginner learn this technique and will also maintain proficiency in the experienced user.

PNEUMATONOMETER

The pneumatonometer (Fig. 6–2E) also relies on the Mackay-Marg principle. Unlike the Tonopen, however, the sensor in the pneumatonometer is air pressure⁷⁰ (Fig. 6–5). The sensing unit of the pneumatonometer, covered with a Silastic diaphragm, consists of a nozzle that is 6 mm in diameter with a central, 2 mm chamber. Pressurized air flows constantly through an opening in the central chamber into the space between the nozzle and the diaphragm. When the sensing unit is not in contact with the eye, the air passes without resistance between the nozzle and the diaphragm to the atmosphere through the exhaust. When the sensing unit does contact the eye, IOP reduces the space between the nozzle and the diaphragm, thereby increasing the resistance to air movement into the atmosphere. This raises the pressure of the air stream in the central chamber, and this increment is converted into IOP. A red mark on the sensing unit shaft helps the operator apply the tip to the cornea with a consistent level of force, as dictated by the instrument's calibration.

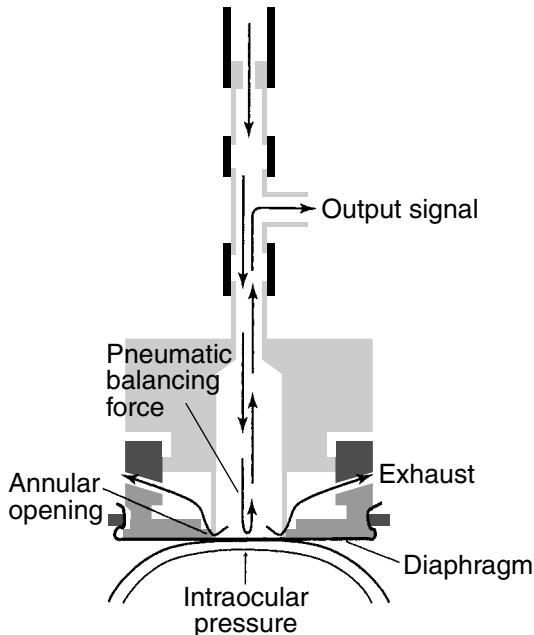


FIGURE 6–5 Pneumatic tonometry. Air introduced into the central chamber escapes through the annular opening between the diaphragm and the bottom of the central chamber and into the exhaust outlet. Contact between the cornea and the diaphragm reduces the size of this opening and the force of this contact is proportional to the IOP. A smaller annular opening, corresponding to increased IOP, limits the escape of air to the exhaust and raises pressure in the central chamber. A pressure transducer connected to the output signal measures this air pressure, and hence, the intraocular pressure. (Modified from Durham DG, Biglano RP, Masino JA. Pneumatic applanation tonometry. *Trans Am Acad Ophthalmol Otolaryngol* 1965;69:1029–1047.)

The pneumatonometer tends to read higher than the Goldmann tonometer, although correlation between the two instruments is generally good.⁷¹ The pneumatonometer can also continuously monitor IOP and ocular pulse, and thus can be useful in the diagnosis and management of carotid-cavernous fistula.⁷² Some authors have suggested that the pneumatonometer is the best tonometer for measuring IOP in infants and young children.⁶¹

SCHIØTZ TONOMETER

The Schiøtz tonometer is the prototypical indentation tonometer (Fig. 6–2F). It consists of a mechanical plunger surrounded by a sleeve, which is attached to a lever (Fig. 6–6). The movement of the plunger in relation to the sleeve as it contacts the cornea deflects the lever, causing its other end to move along a scale, which indirectly indicates IOP. However, the IOP that the Schiøtz tonometer measures is actually the eye pressure that results when the tonometer is in contact with the eye, and is called P_t . P_t is higher than the "real" IOP in the eye, known as P_o ,

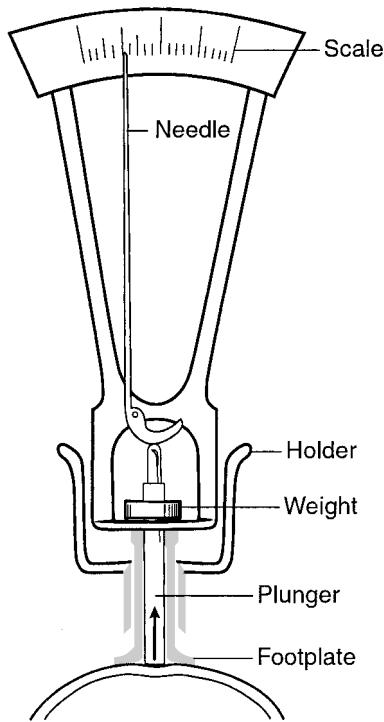


FIGURE 6-6 Cutaway view showing basic features of Schiøtz-type indentation tonometer. Higher intraocular pressure (IOP) allows less movement of the plunger in relation to the foot plate, producing less deflection of the needle and a lower scale reading. Lower IOP allows the plunger to move downward in relation to the foot plate, increasing deflection of the needle to the right and a higher scale reading. (From Hoskins HD, Kass MA. *Becker-Shaffer's Diagnosis and Therapy of the Glaucomas*. 6th ed. St. Louis, Mo: CV Mosby; 1989:77.)

because the tonometer has indented the cornea, reducing the ocular volume and increasing the pressure within the eye. The relationship between P_t and P_o varies from eye to eye and depends on the rigidity of the cornea and sclera. The conversion tables of Friedenwald take into account scleral rigidity and allow the calculation of an IOP in mm Hg from the P_t scale reading.

Schiøtz tonometry must be performed with the patient supine. Following application of a topical anesthetic, the plunger is oriented perpendicular to the center of the cornea and gently lowered until the sleeve rests on the eye. If the scale reading is less than 4, additional weights provided with the tonometer are added to the plunger to increase its weight from 5.5 to 7.5 or 10.0 g.

Until the development of hand-held applanation tonometers, and particularly the Tonopen, the main advantage of the Schiøtz tonometer was its portability. Disadvantages of the Schiøtz tonometer include measurement errors related to differences in scleral rigidity and corneal curvature, the requirement that the patient be prone, the possibility of corneal trauma, and the fact that repeated measurements can lower IOP.

NONCONTACT (AIR PUFF) TONOMETER

As its name suggests, the noncontact tonometer measures the IOP without an instrument touching the cornea. A collimated beam of light is directed to the corneal apex, as is a receiver to detect parallel, coaxial rays of this light reflected from the cornea (Fig. 6-7). After proper alignment, a jet of air directed at the corneal apex flattens the cornea. Given that parallel light rays will remain parallel after reflecting off a planar surface, peak intensity of the reflected light signifies complete flattening of the cornea. Because the force of the jet of air increases linearly with time, the interval required to flatten the cornea, or produce maximum light reflection, becomes a measurement of the IOP. These time intervals, calibrated against measurements with the Goldmann tonometer, are converted to mm Hg and digitally displayed.

The noncontact tonometer is accurate within the range of "normal" IOPs but less so at higher pressures and in eyes with abnormal corneas.⁶⁴ Because this tonometer samples pressure over an extremely short time period (1 to 3 msec), readings may vary widely, depending upon the phase of the ocular pulse. Therefore, the mean of multiple measurements provides a more accurate IOP. A portable, noncontact tonometer, the Pulsair, is available and appears to function similarly to the stationary models.

The noncontact tonometer can be used without an anesthetic and eliminates the risk of transmitting infectious agents from one eye to another via the tonometer tip. The force of the air jet, however, can aerosolize the tear film and may theoretically transmit viruses by an airborne route.⁷³

SELF-TONOMETER

Zeimer has developed an applanation tonometer that can be used by patients at home. The applanation is detected optically by monitoring the amount of light reflected from a flexible membrane that comes in contact with the cornea and to which an increasing air pressure is applied (Fig. 6-8). This system aligns the probe perpendicular to the apex of the cornea and measures the air pressure necessary to applanate the cornea. The self-tonometer has good reproducibility, correlates well with the Goldmann tonometer, and allows IOP determination at any time of the day or night, depending upon the patient's need. However, it does require a highly motivated patient and carries a small risk of causing a corneal abrasion.^{74,75}

MAKLAKOV TONOMETER

This is an applanation tonometer that applies a fixed weight to the cornea, measures the area of the applanated surface, and calculates the IOP from the size of the area applanated. This constant force tonometer differs from

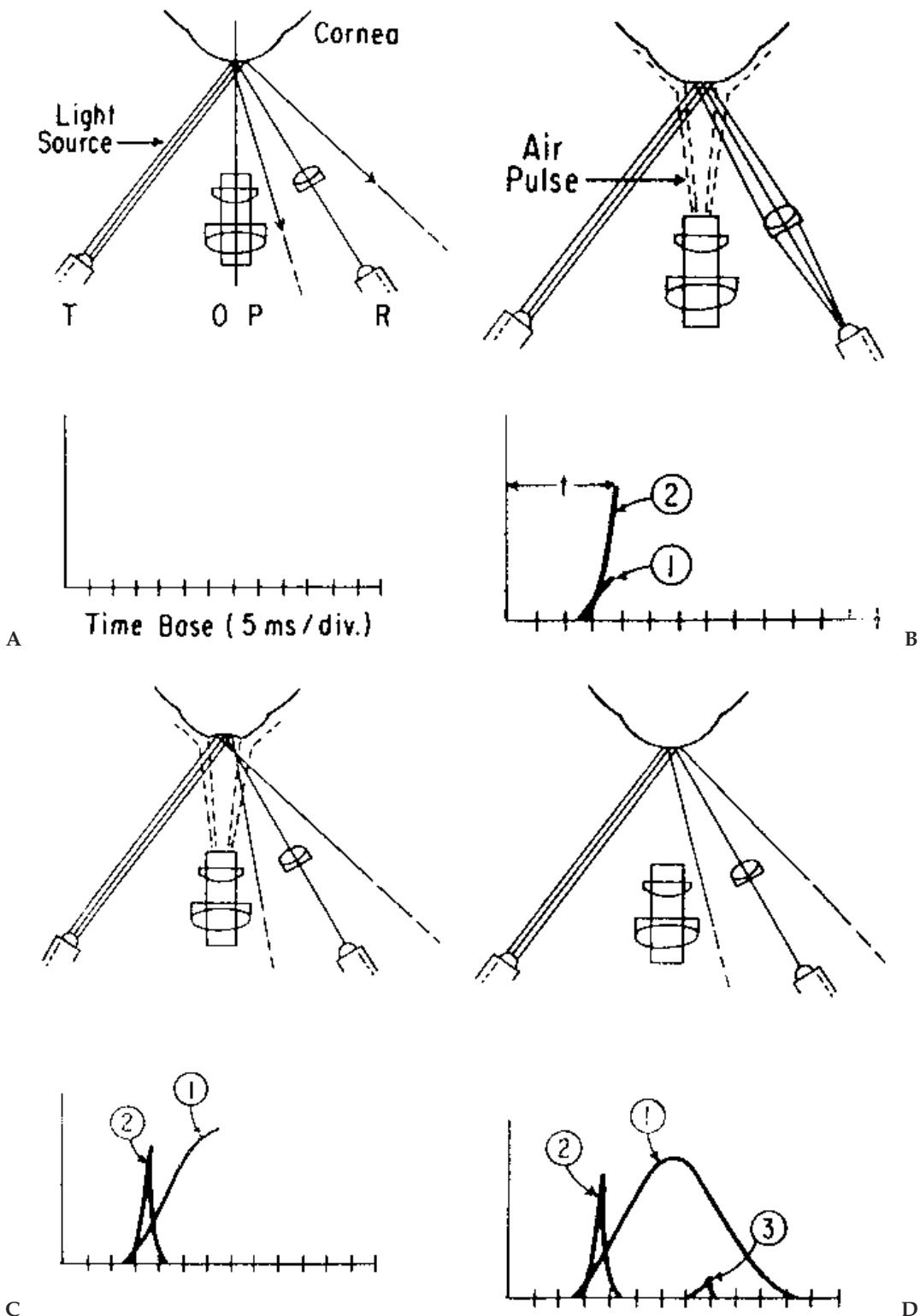


FIGURE 6-7 Noncontact tonometry. (A) While the cornea is aligned with optical system (O), a light source from the transmitter (T) reflects from the cornea toward the receiver (R). (B) An air pulse (1) applanates the cornea and allows the maximum number of light rays (2) to be received and detected by R. The time interval (t) between an internal reference point to the moment of applanation is converted to intraocular pressure and displayed in millimeters of mercury. (C) Continued air pulse momentarily indents the cornea, reducing the number of rays received by R. (D) As the cornea returns to a normal curvature, a second moment of applanation causes another light peak (3). (From Shields MB. The noncontact tonometer: its value and limitations. *Surv Ophthalmol* 1980;24:211-219; modified from Grolman B. A new tonometer system. *Am J Optom Arch Am Acad Optom* 1972;49:646-660.)



FIGURE 6-8 A self-tonometer in use, showing patient resting her orbit on the eye cup prior to activating the instrument.

the Goldmann tonometer in which a variable force is used to flatten a constant area.⁴

ABNORMAL CORNEAS

Application of Goldmann and Schiøtz tonometers to irregular or scarred corneas can produce unreliable IOP measurements. Pooling of fluorescein and corneal edema may contribute to inaccuracies with the Goldmann tonometer, and the Schiøtz tonometer was designed for normal corneas with normal curvatures and is not accurate in these abnormal situations.⁷⁶ Early studies in patients with scarred and edematous corneas⁷⁶ and in monkeys with corneal edema⁷⁷ established that the MacKay-Marg tonometer was superior to both the Goldmann and the Schiøtz in these eyes. Subsequent evaluations of newer tonometers indicate that the pneumatonometer and Tonopen are comparable to the MacKay-Marg in eyes with irregular corneas^{78,79} and in eyes shortly after penetrating keratoplasty.⁸⁰

CORNEAL THICKNESS

Corneal thickness can affect IOP measurements obtained with the applanation tonometer⁸¹ and the Tonopen.⁸² Simultaneous manometry and hand-held applanation tonometry have shown that tonometry underestimated IOP in eyes with thin corneas and overestimated pressure in eyes with thick corneas.⁸³ Linear regression analysis of a population-based study showed that IOP increased nearly 0.20 mm Hg with each 10 μ increase in central corneal thickness.⁸¹ Furthermore, mean central corneal thickness was greatest in the ocular hypertensive patients and least in those with glaucoma, with the control subjects in between.⁸⁴ Other studies^{85,86} have demonstrated less corneal thickness in normal-tension glaucoma patients compared with patients with primary open-angle glaucoma and higher

IOPs, consistent with the hypothesis that low IOP measurements in some normal-tension glaucoma patients may result from thinner corneas rather than actually lower pressures. Important findings from the Ocular Hypertension Treatment Study (OHTS) concerning corneal thickness have recently been published.^{87,87a} Brandt et al.⁸⁷ found that subjects in the OHTS had a mean corneal thickness of 573 μ m significantly greater than that in the normal population, and that African-American subjects had thinner central corneas than the white subjects in the study (556 μ m vs. 579 μ m, respectively). Gordon et al.^{87a} demonstrated that central corneal thickness was a powerful predictor of the development of glaucoma. These authors recommend the measurement of central corneal thickness in the clinical evaluation of patients with ocular hypertension.

REFRACTIVE SURGERY

IOP, measured by both Goldmann applanation and noncontact tonometry, has been reported to decrease after excimer laser photorefractive keratectomy (PRK). Chatterjee et al., comparing IOP by noncontact tonometry in 1320 eyes following PRK with their fellow eyes that were about to undergo PRK, found consistently lower pressures in the treated eyes.⁸⁸ This decrease in IOP correlated with the extent of myopia treated, suggesting that the effect on IOP measurement resulted from thinning of the central cornea.

The effect of radial keratotomy on IOP is less clear. Although a retrospective analysis from Canada showed a small (1.0 mm Hg) but statistically significant pressure decrease by applanation tonometry following radial keratotomy,⁸⁹ the Prospective Evaluation of Radial Keratotomy (PERK) study found no IOP difference between unoperated and operated eyes during the first year following surgery.⁹⁰

SPECIAL CONSIDERATION

A practitioner evaluating glaucoma in eyes after laser vision correction must consider that the decreased corneal thickness will reduce the Goldmann tonometer measurement, as compared with actual IOP.

STERILIZATION OF TONOMETER TIPS

Because the same instrument is used to measure IOP on multiple patients, tonometers are a prime vehicle for cross-infections, especially viral.⁹¹ Therefore, adequate disinfection between patients is critical. Most of this concern involves the prism of the Goldmann tonometer. Both the Centers for Disease Control and the American Academy of

Ophthalmology, in conjunction with the National Society for the Prevention of Blindness and the Contact Lens Association of Ophthalmologists, recommend wiping the tonometer tip clean and then disinfecting it with a 5-minute soak in either a 1:10 dilution of sodium hypochlorite (household bleach), 70% isopropyl alcohol, or 3% hydrogen peroxide.⁹¹ The American Academy of Ophthalmology recommendation also includes the option of using a 70% isopropyl alcohol swab to wipe the tip.⁹² However, while soaks in 70% isopropyl alcohol or 3% hydrogen peroxide are effective in reducing hepatitis C virus from tonometer tips, alcohol swabs are not.⁹³ The disadvantages of all these protocols are that they do not eradicate *Acanthamoeba*, repeated use may damage the tonometer prism, and incomplete removal of disinfectant can lead to iatrogenic injury to the cornea and ocular surface.

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AQUEOUS HUMOR DYNAMICS

Carol B. Toris, Ph.D.

Aqueous humor dynamics is the study of the parameters that maintain intraocular pressure (IOP). These parameters include aqueous production by the ciliary processes and aqueous outflow through the uveoscleral and trabecular pathways. Trabecular outflow depends on resistance in the trabecular meshwork and pressure in the aqueous drainage vessels, the episcleral veins.

Various methods to study these parameters have been developed for clinical and research use. All of these methods have assumptions and inherent problems, they provide invaluable information regarding aqueous humor dynamics and the regulation of IOP.

Fluorophotometry determines the rate of aqueous flow through the anterior chamber by measuring the clearance of externally applied fluorescein from the cornea and anterior chamber. This provides an estimate of aqueous production. Several devices exist for determining episcleral venous pressure. This pressure changes little under most circumstances. Outflow resistance is usually determined by measuring its inverse, the facility of aqueous outflow. Standard tonography provides a relatively rapid assessment of this value, but is subject to potential sources of error, including pseudofacility and changes in ocular rigidity. Although use of fluorophotometry to determine outflow facility avoids these errors, it is time consuming and probably too cumbersome for routine clinical practice. Currently, uveoscleral outflow must be calculated as the difference between aqueous flow and trabecular outflow.

The majority of these techniques are not used in routine clinical practice. However, they appear often in research protocols. Understanding these tests and their principles will significantly enhance the appreciation of how glaucoma drugs affect aqueous humor dynamics.

BACKGROUND

In simplest terms, steady state IOP occurs when the rate of aqueous humor production equals its outflow. Thus, flow into the eye equals or approximates flow out of the eye. Because of the practical difficulties of measuring actual aqueous humor production, analyses of aqueous humor dynamics are considered in terms of aqueous flow (F_a).

Early investigations of the factors governing aqueous humor outflow concentrated on flow through the trabecular meshwork, into Schlemm's canal, and into the episcleral veins. Such flow is directly proportionate to the pressure drop across this outflow mechanism, or IOP minus the episcleral venous pressure ($IOP - P_V$). It is also inversely related to the resistance to outflow (R). The mathematical expression of these relationships is:

$$F_a = \frac{IOP - P_V}{R} \quad (1)$$

By invoking a coefficient of outflow facility (C_{trab}), the proportionality of aqueous flow to the pressure drop across the trabecular meshwork can be converted to another equation:

$$F_a = C_{trab}(IOP - P_V) \quad (2)$$

Comparing these two equations reveals that outflow facility and resistance are inversely related ($C_{trab} = 1/R$). Solving equation (2) for the IOP yields the Goldmann equation, which displays the main factors that determine IOP.

$$IOP = \frac{F_a}{C_{trab}} + P_V \quad (3)$$

Here, IOP is intraocular pressure in mm Hg, F_a is the rate of aqueous flow in $\mu\text{L}/\text{min}$, C_{trab} is the facility of trabecular outflow in $\mu\text{L}/\text{min}/\text{mm Hg}$, and P_V is the pressure in the episcleral veins in mm Hg.

We now know that aqueous drains through the uveoscleral pathway (F_{us}) as well as through the trabecular outflow pathway (F_{trab}). Aqueous flow must be the sum of aqueous drainage through both outflow pathways. Hence:

$$F_a = F_{us} + F_{\text{trab}}. \quad (4)$$

In light of this, and equation (2), aqueous flow through the anterior chamber can be represented by the following equation:

$$F_a = F_{us} + C_{\text{trab}}(\text{IOP} - P_V). \quad (5)$$

Any thorough assessment of aqueous humor dynamics requires the evaluation of each of these parameters.

TECHNIQUES FOR MEASURING INTRAOCULAR PRESSURE

TONOMETRY

Tonometry measures IOP indirectly and noninvasively. All tonometers measure the force required to deform the cornea in a specific way. Because this force is coupled to the pressure within the anterior chamber, such a measurement, when properly calibrated, can be used to determine the IOP. Tonometers fall into two categories: applanation, which measures the force necessary to flatten a known surface area of cornea; and indentation, which measures the extent to which an externally applied standard weight will deform the globe. Chapter 6 discusses in detail all of the main forms of tonometry and their principles of function.

Applanation Tonometry

Applanation tonometers include the Goldmann tonometer, the Perkins tonometer, the MacKay-Marg tonometer, the Tonopen, and the pneumatic tonometer. Goldmann tonometry is the international standard for measuring IOP. This tonometer uses a plastic tip connected to a spring, which supplies the force for flattening the cornea. The force is adjusted manually by a knob that contains a scale indicating the force applied in grams. When the cornea is applanated 3.06 mm in diameter, the IOP in mm Hg is equal to the force exerted by the tonometer in grams, multiplied by 10.

Applanation of the cornea displaces only 0.5 μL of fluid from the eye. Because this produces only a negligible elevation of the IOP, the inherent rigidity of the cornea and sclera influences the measurement only slightly.

SPECIAL CONSIDERATION

When using the Goldmann tonometer during fluorophotometry, the fluorescein can be replaced with condensed milk. This will not interfere with the fluorescence signal sent to the detector.¹

The Perkins tonometer works on the same principle as the Goldmann tonometer, yet it is packaged as a portable, handheld device. The battery-operated light source and counterbalance make it usable in the vertical and horizontal position, allowing the examiner to measure pressures in patients who cannot sit at a slit-lamp.²

The MacKay-Marg tonometer³ applanates with a plunger that moves within a sleeve. Applanation of the tip to the cornea moves this plunger relative to the sleeve, and the extent of deflection is detected by a transducer connected to the plunger and recorded on a moving strip of paper. After an initial pressure increase, the strip recording decreases to the level of IOP. Multiple readings are averaged to obtain the final pressure reading. This tonometer, which applanates a relatively small area, is useful in eyes with edematous or irregular corneas but is no longer manufactured.⁴ The widely available Tonopen, a miniaturized electronic portable applanation tonometer, works on a similar principle.⁵

The pneumatic tonometer⁶ consists of a gas-filled chamber with a transducer capable of sensing the pressure within the chamber. Gas flows into the sensor at a constant rate and exits into the atmosphere through exhaust channels via an annular opening in the membrane covered tip. Pressing the membrane against the cornea progressively restricts this opening, increasing the pressure in the chamber, which is detected by the sensor. Applanation occurs when the pressure within the chamber equals the IOP. This tonometer also indents a smaller area of cornea than the Goldmann tonometer. The pneumatic tonometer can be used to measure both IOP and outflow facility, as discussed in the following text (Fig. 7-1).

Indentation Tonometry

The Schiøtz tonometer is an indentation tonometer. It registers the depth of indentation of the anesthetized cornea produced by the known weight of the instrument. The weight is carried on a plunger, which moves toward the eye relative to a surrounding sleeve that rests on the cornea. This movement produces deflection of a pointer along a calibrated scale. Because the extent of plunger movement is counterbalanced by the force of the IOP, the scale reading will reflect the IOP.



FIGURE 7-1 A pneumatic tonometer can be used to measure either intraocular pressure or outflow facility. For tonometry, the patient is usually seated, but can be supine. For tonography, the patient is supine, with the lids held open without applying pressure to the globe. A 10 g weight is attached to the piston of the tonometer sensor, and the sensor is positioned perpendicularly on the anesthetized central cornea until the piston slides into the sensor to the black indicator line. This position is maintained for either 2 or 4 minutes while intraocular pressure is continuously monitored. The rate of decrease of intraocular pressure is related to the outflow facility.

Each unit on this scale corresponds to an indentation of 1/20 of a millimeter in the cornea. A higher IOP produces relatively less movement of the pointer and a lower scale reading. If the scale reading is less than 4, an additional weight is applied and the measurement is repeated. Pointer scale readings for the weight applied are converted to IOP in units of mm Hg using standard tables.

Schiøtz tonometry displaces 15 to 20 μL of aqueous humor, much more than the 0.5 μL displaced by the Goldmann tonometer. Because of this volume displacement, measurements with this instrument are subject to errors induced by ocular rigidity. Eyes with reduced ocular rigidity (increased elasticity) may dissipate the weight of the Schiøtz tonometer, resulting in less resistance to corneal indentation, greater movement of the plunger, and underestimation of IOP. Conversely, increased ocular rigidity will diminish plunger movement and produce an overestimate of the IOP.

DIRECT MEASUREMENT OF INTRAOCULAR PRESSURE

Direct measurement of IOP relies on cannulation of the anterior chamber with a needle connected to a pressure transducer that measures the pressure at the tip of the needle. A second needle, connected to a fluid-filled reservoir, can allow experimental adjustment of IOP, as determined by the height of the reservoir above the eye. This invasive method is rarely used in the living human eye.

TECHNIQUES FOR MEASURING AQUEOUS FLOW

Clinical assessment of aqueous humor production by the ciliary processes is not possible. However, measuring aqueous flow through the anterior chamber provides a close estimation of aqueous production. Aqueous flow is defined as the rate of movement of aqueous humor from the posterior chamber through the pupil and into the anterior chamber. It does not include the flow of aqueous by any other route. Because unknown, small amounts of aqueous humor probably do escape these other routes, aqueous flow does not exactly equal aqueous production.

PEARL... Clinical measurement of aqueous humor flow from the posterior chamber through the pupil and into the anterior chamber provides a close approximation of the rate of aqueous production by the ciliary processes.

Fluorophotometry, which measures the disappearance rate of fluorescein from the anterior chamber, is the most widely used method to measure aqueous flow.⁷ Fluorescein is administered to the eye, either by corneal iontophoresis⁸ or, more commonly, by multiple drop application.⁹ A small fraction of each drop enters the corneal stroma through the epithelium. The rest of the drop is washed away by the flow of tears. Over time, the fluorescein traverses the corneal stroma and crosses the endothelium. Because the corneal endothelium is much more permeable to small, water-soluble organic molecules than the epithelium, the fluorescein does not return to the surface of the eye. Instead, it is gradually released into the anterior chamber from the resulting depot in the corneal stroma.

Inside the anterior chamber, the fluorescein mixes with aqueous humor by normal thermoconvective currents. From the anterior chamber, the fluorescein predominantly leaves the eye along with the aqueous humor into which it is dissolved. At least 95% of the topically applied fluorescein that enters the anterior chamber is cleared as a result of bulk outflow of aqueous humor through the iridocorneal angle.¹⁰⁻¹³ Because of this, the rate of disappearance of the intracameral fluorescein provides a good estimate of the rate of aqueous flow.

PEARL... In preparing for fluorophotometry, younger subjects require more drops of fluorescein than older subjects to assure a measurable concentration in the anterior chamber throughout the measurement period.

When an equilibrium has been established, the concentrations of fluorescein in the corneal stroma and the anterior chamber decrease over time. The rate of this

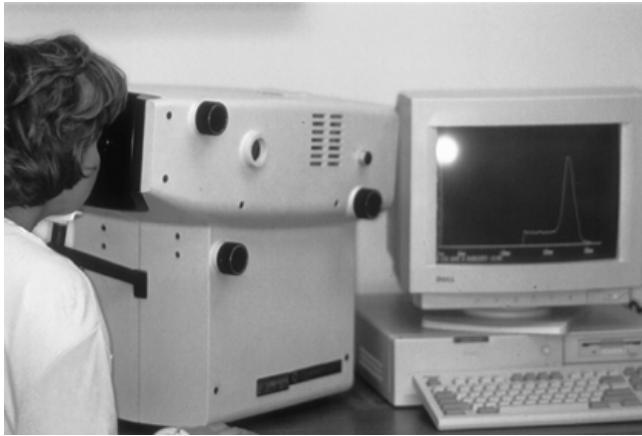


FIGURE 7-2 A fluorophotometer. This instrument consists of an optical head controlled by a computer. The patient is positioned in front of the eyepiece so that the pupil is centered on the adjustment target and the cornea is in the focal plane. A scan is made from the corneal epithelium through the anterior chamber, and the fluorescein concentration (ng/mL) is plotted against distance (mm).

decrease depends on the rate of aqueous flow. These concentrations are measured by a fluorophotometer (Fig. 7-2). In this instrument, an optical system focuses an excitation beam of blue light on a small, defined region of the eye and collects the emitted fluorescent signal from the same region. The excitation beam and the light pathway of the detector are oriented at an angle to each other, and their intersection, the focal diamond, is scanned across a contiguous series of volume elements within the eye. Scans are made in a sequence of steps from the central cornea through the anterior chamber. The signal, collected by a photomultiplier tube, is sent to a recorder and converted into concentration units (ng/mL) by reference to a standard curve.

Scans of the cornea and anterior chamber are repeated at 45- to 60-minute intervals for several hours to construct a good set of fluorescein decay curves (Fig. 7-3). Scans collected at intervals shorter than 30 minutes may not provide an accurate measure of aqueous flow because of the limits on the precision of the instrument and the slow rate of loss of fluorescein from the eye.¹⁴

PEARL... In sleep studies, fluorophotometry scans are collected at intervals of several hours, rather than the usual interval of 45 to 60 minutes. This reduces the number of disturbances to the subject and the possibility that the measurement will affect the results.¹⁵

Fluorophotometry works by measuring the rate of fluorescein removal (or clearance) from the eye. This requires knowledge of the mass of fluorescein in the eye, which depends on the corneal and anterior chamber volumes. Corneal volume varies little among healthy human adults and generally is assumed to equal 70 μL .⁷ In contrast, the

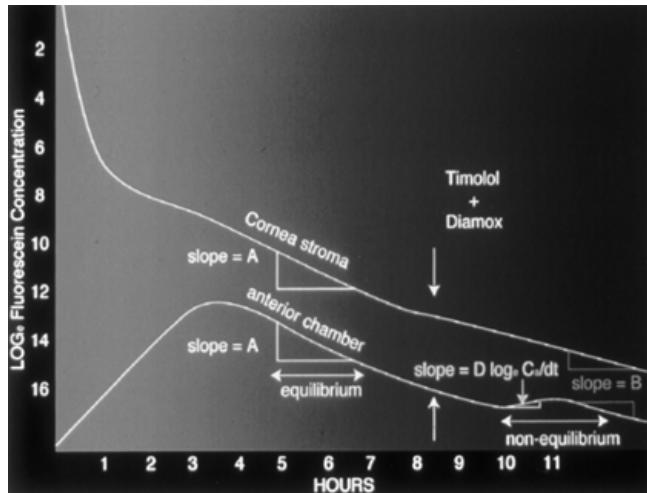


FIGURE 7-3 Time course of fluorescein concentration in the corneal stroma and anterior chamber after topical administration. The curves are generated from four to seven measurements taken by a fluorophotometer at 45- to 60-minute intervals. At equilibrium, the absolute value of the slopes of the fluorescein decay curves for both the cornea and the anterior chamber are the same (slope A). Baseline aqueous flow is calculated from the equilibrium data when the cornea and anterior chamber decay curves are parallel. For measuring outflow facility, oral acetazolamide and topical timolol are administered. These drugs are aqueous flow suppressants, causing a reduction in the slope of the fluorescein decay curves (slope B), from which a new aqueous flow is calculated. Intraocular pressure is measured at the beginning and end of each aqueous flow determination. Trabecular outflow facility is calculated from equation 10 in the text. (Redrawn from Toris CB, Yablonski ME, Tamesis R. Aqueous humor dynamics. In: Choplin NT, Lundy DC, eds. *Atlas of Glaucoma*. London: Martin Dunitz Ltd.; 1998, with permission.)

anterior chamber volume varies greatly among individuals and must be determined for each eye. This is measured in one of two ways. One method measures the central corneal thickness and the diameter and depth of the anterior chamber, and then calculates the anterior chamber volume on the assumption that its geometry is approximated by a spherical segment.¹⁶ Another method calculates the volume as a series of cylindrical sections from a Polaroid photograph of an optical cross-section of the anterior chamber.¹⁷

Figure 7-3 depicts the behavior of the concentrations of fluorescein in the anterior segment of the eye over time. The rate of aqueous flow determines the slope of the fluorescein decay curves for both the cornea and anterior chamber and the distance between them. On a logarithmic scale, these curves are linear during equilibrium, and their slopes are the same.

The aqueous flow rate (F_a) is a function of the anterior chamber volume (V_{ac}), the slope of the decay curves (A), and the ratio of the mass of fluorescein in the corneal stroma to that in the anterior chamber (M_{cs}/M_{ac})

$$F_a = V_{ac} A [1 + M_{cs}/M_{ac}] \quad (6)$$

M_{cs} can be rewritten as $V_{cs}C_{cs}$, where C_{cs} is the fluorescein concentration of the corneal stroma and V_{cs} is its volume. Similarly, M_{ac} can be rewritten as $V_{ac}C_{ac}$. Equation 6 then becomes

$$F_a = V_{ac}A[1 + V_{cs}C_{cs}/V_{ac}C_{ac}]. \quad (7)$$

Assuming that V_{cs} and V_{ac} remain constant in the steady state, F_a becomes a function of the distance between the two parallel decay curves (the logarithm of C_{cs}/C_{ac}) and their slope (A). At equilibrium, C_{cs}/C_{ac} does not change over time. The more rapid the rate of aqueous flow (F_a), the steeper will be the slope of the decay curves (A) and the larger the magnitude of the distance between the two curves (C_{cs}/C_{ac}). At the other extreme, if the rate of aqueous flow ceases ($F_a = 0$), the fluorescein concentrations in the anterior chamber and corneal stroma will equalize by diffusion and the decay curves will be flat ($A = 0$).¹⁸

The fluorophotometric measurement of aqueous flow employs several assumptions:

1. The fluorescein is evenly distributed in the anterior chamber. After topical application, the examiner must wait at least 4 hours for the fluorescein to become well mixed into the aqueous humor. Measurements taken before this time could produce erroneous calculations of aqueous flow.
2. There is minimal diffusional loss of fluorescein into limbal or iridial vessels or into the vitreous cavity. This method does not work in eyes with aphakia, pseudophakia, an iridectomy, or any condition in which fluorescein can exit the eye by means other than through the physiological chamber angle outflow pathways.
3. There are no optical obstructions that could cause light scatter. The light scatter caused by corneal opacities or severe uveitis interferes with the fluorescence signal reaching the instrument.

PITFALL... Fluorophotometry does not work in eyes with any condition in which fluorescein can exit the eye by means other than through the physiological anterior chamber angle outflow pathways.

TECHNIQUES FOR MEASURING EPISCLERAL VENOUS PRESSURE

In the human eye, aqueous humor leaves the canal of Schlemm and enters the venous network that encircles the sclera near the corneal limbus. The pressure in these episcleral veins is determined by vasoactive and gravitational factors. It is largely independent of IOP and the flow of aqueous humor, even though it is one of the major determinants of the steady-state pressure of the eye.

All methods described for measuring episcleral venous pressure in humans rely on identifying the aqueous veins on the surface of the eye. Pressure is applied to the area of the sclera occupied by these veins until the veins indent or collapse. The methods of applying this pressure include a rigid device, a jet of air, and a flexible membrane.¹⁹ A commercially available flexible membrane venomanometer (EyeTech, Morton Grove, IL) attaches directly to a Haag-Streit slit-lamp (Fig. 7-4).

All of these methods are generally restricted to research studies because it is difficult to identify an appropriate vessel, and the end point of vessel collapse is highly subjective. Preferably, two experienced individuals perform these measurements. One determines the end point while the second records the results in a masked fashion. The measurement is repeated two to three times and the results averaged for a final value.

PITFALL... When episcleral venous pressure is measured with a venomanometer, the most visible vessels are often not episcleral veins. Using collapse of one of these large veins as an end point will overestimate the actual episcleral venous pressure.

Although some situations do alter episcleral venous pressure, such as inhalation of O₂,²⁰ application of cold

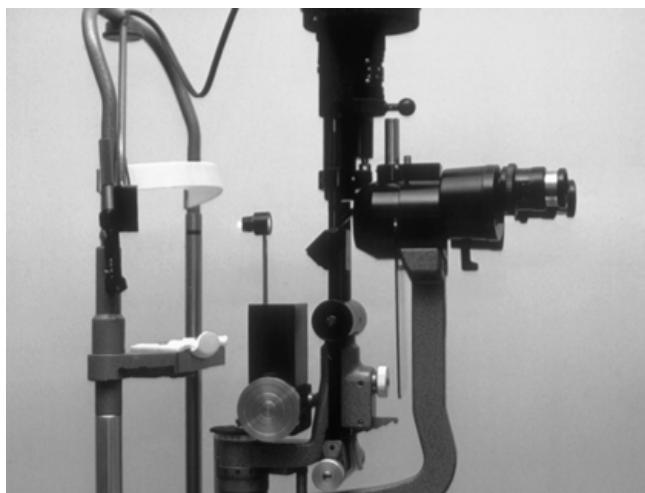


FIGURE 7-4 A venomanometer. This commercially available instrument is bolted to a Haag-Streit slit-lamp. The patient's head is positioned in the chin rest but rotated slightly to one side with gaze directed to the same side. This allows the operator to visualize the temporal corneoscleral limbus while looking through the instrument probe and binocular eyepieces of the slit-lamp. The aiming ring incorporated in the flexible membrane is flattened on the sclera, and the surface vessels are brought into focus. The knob on the side of the instrument is rotated to increase the pressure behind the membrane until the observer notes the initial blanching of any blood vessel in the field of view. The reading on the scale indicates pressure in mm Hg.

temperature,²¹ and drug treatment,²² this pressure is usually relatively stable and its magnitude of change is relatively small. Most clinical studies of aqueous humor dynamics are interpreted without accurately measured values of episcleral venous pressure. These studies will assume that episcleral venous pressure is in the range of 6 to 10 mm Hg if the subject is sitting up. Changes in actual episcleral venous pressure during the course of a study could produce erroneous conclusions concerning the rates of uveoscleral and trabecular outflow (equation 5), and the cause of the IOP change.

Direct cannulation can provide the most accurate measurements of episcleral venous pressure. This method is used in experimental animals only and is technically difficult. However, such measurements have yielded important information about the interrelationship between IOP and episcleral venous pressure.²³

TECHNIQUES FOR MEASURING TRABECULAR OUTFLOW FACILITY

As stated by Grant, outflow facility "represents the rate at which fluid can be expressed from the eye by pressure."²⁴ In other words, facility is a measure of the ease by which aqueous leaves the eye, and, as stated earlier, it is the inverse of outflow resistance. It is generally agreed that the trabecular meshwork and the inner wall of Schlemm's canal provide most of this resistance. A decrease in this resistance (increase in facility) reduces the IOP.

Two ways to measure trabecular outflow facility in the living human eye are tonography and fluorophotometry. Both methods compare aqueous flow at one pressure to that at another pressure. With tonography, a tonometer is used to provide an external force on the eye. This increases the IOP. The degradation of the tonometer readings over time, with the aid of standard tables, provides a measure of volume displacement, or flow. In contrast, the fluorophotometric method measures aqueous flow, as described above, at two different pressure levels, achieved using an oral or topical aqueous flow suppressant. A third method, invasive tonography, relies on direct measurement of aqueous flow in a cannulated eye, and varying the IOP by changing the height of a fluid-filled reservoir attached to the cannula.

TONOGRAPHIC METHOD

Tonography has been the most widely used method to measure outflow facility and was once employed as a routine clinical test. Although tonography is now used mainly for research purposes, it has provided valuable information about the pathophysiology of glaucoma and is still used to understand how treatment modalities lower IOP.

Tonography involves placing a weighted tonometer on the anesthetized cornea of the recumbent patient for 2 or 4 minutes (see Fig. 7-1). The standard weight applied to the cornea increases IOP and aqueous drainage through the trabecular meshwork. The IOP decreases during the test as fluid is pressed out of the eye. Using the reference tables developed by Friedenwald,²⁵ the change in the IOP provides the inferred volume of aqueous humor displaced from the eye during the measurement. If it is assumed that fluid displaced from the eye by the weight of the tonometer, ΔV , is the only factor to account for the IOP decrease, then the rate of fluid outflow from the eye is $\Delta V/t$. Tonographic outflow facility, C_{ton} , is then calculated from Grant's equation²⁴:

$$C_{\text{ton}} = \frac{\frac{\Delta V}{t}}{IOP_t - IOP_0} \quad (8)$$

In this equation, IOP_0 is the IOP at time 0, before the weighted tonometer is applied to the eye. Here inflow and outflow of aqueous humor are equal, IOP is constant, and intraocular volume is stable. IOP_t is the average IOP at the end of the test (time t), when the rate of aqueous outflow from the eye is greater than inflow and the ocular volume has diminished.

The greater the IOP decrease, the greater the expected volume change and the larger the trabecular outflow facility. The relationship between corneal indentation and IOP assumes a normal ocular rigidity and corneal curvature. Deviations from this assumption can produce erroneous tonographic results, as discussed in the following text.

Tonography assumes that the weight applied to the eye does not affect the rate of aqueous humor production (inflow), and that the change in pressure during the measurement results entirely from fluid being forced out of the eye across the trabecular meshwork. Any egress of fluid by nontrabecular routes, or decrease in the rate of aqueous humor formation, as may result from a decrease in ocular blood volume or extracellular fluid volume, would be measured as increased outflow facility. This artificial increase in measured facility has been termed pseudofacility.

From these considerations, outflow facility measured by tonography (C_{ton}) is actually the sum of the trabecular outflow facility (C_{trab}), pseudofacility (C_{ps}), and the facility of outflow through the uveoscleral pathway (C_{us}), the latter of which is considered to be negligible under most circumstances.

$$C_{\text{ton}} = C_{\text{trab}} + C_{\text{ps}} + C_{\text{us}} \quad (9)$$

When tonography is performed with an indentation tonometer, the measured pressure (and volume) change as a function of time is based on the assumption that the ocular rigidity coefficient is accurate, both at the beginning

and throughout the test. However, tonography makes no compensation for potentially large individual variations in ocular rigidity. Because this method relies on the weight of the tonometer to indent the eye, variations in ocular rigidity can be a potential confounding factor in this measurement. In contrast, the pneumatic tonography unit minimizes the influence of ocular rigidity because it creates a relatively small indentation of the cornea. Both instruments derive a change in ocular fluid volume from standard tables and neither compensates for changes in pseudofacility.

FLUOROPHOTOMETRIC METHOD

The fluorophotometric assessment of outflow facility avoids the problem of pseudofacility.²⁶ Although this method also induces a change in IOP, it differs from tonography in that it directly measures the change in ocular fluid flow rather than inferring the change from the measured IOP and standard tables.

First, tonometry and fluorophotometry are used to determine IOP (IOP_1) and aqueous flow (F_{a1}). Next, the patient is given a drug to reduce aqueous flow and IOP. Figure 7-3 illustrates the effect of this reduction in aqueous flow on the fluorescein decay curves in the cornea and anterior chamber. Once the drug has taken effect, IOP and aqueous flow are remeasured (IOP_2 and F_{a2} , respectively) and equation 10 is used to calculate outflow facility. Outflow facility determined by fluorophotometry is referred to as C_{f1} to distinguish it from outflow facility determined by other methods.

$$C_{f1} = \frac{F_{a1} - F_{a2}}{IOP_1 - IOP_2} \quad (10)$$

Like tonography, this method also rests on several assumptions. It assumes that the entire change in aqueous flow after the administration of the aqueous flow suppressant is caused by an equal decrease in trabecular outflow (i.e., that all other parameters of ocular hydrodynamics are unchanged). The topical beta blocker timolol and the systemic carbonic anhydrase inhibitor acetazolamide work well for this purpose. This method also assumes that uveoscleral outflow facility is very small relative to trabecular outflow facility and varies little with changes in IOP.²⁷⁻²⁹ It is not valid in eyes with any condition that greatly affects uveoscleral outflow facility, such as a cyclo-dialysis cleft.²⁹

Fluorophotometry measures the change in flow across the trabecular meshwork more directly than does tonography, and avoids the problems of pseudofacility and ocular rigidity. In addition, the fluorophotometric method can detect changes in trabecular outflow facility that are missed by tonography.²² However, the six hours needed to complete the determination will probably limit its use as a routine clinical tool.

INVASIVE METHOD

Several invasive methods exist for measuring trabecular outflow facility. The most preferred of these uses two needles inserted into the anterior chamber and connected to a reservoir of mock aqueous humor.³⁰ Aqueous is infused at two different rates (F_{a1} and F_{a2}) to establish two different IOPs (IOP_1 and IOP_2). The resulting values are then used in equation 10 to calculate outflow facility. In addition to being invasive, this method does not avoid the problems of pseudofacility and ocular rigidity.

SPECIAL CONSIDERATION

Currently there is no ideal way to measure outflow facility. Selection of the most appropriate method requires considerations of the model, time factors, the hypothesis to be tested, and other details of the study design.

TECHNIQUES FOR MEASURING UVEOSCLERAL OUTFLOW

In the clinical setting, there is currently no way to measure uveoscleral outflow. However, it can be evaluated indirectly with some success by measuring the parameters that define it and employing the following equation, derived from equation 5.

$$F_{us} = F_a - C_{trab}(IOP - P_V). \quad (11)$$

When determined in this way, uveoscleral outflow can vary considerably because of intrinsic variations in each of the components in this equation. Calculations using facility measured by fluorophotometry may provide more physiological results than calculations using tonographic facility.²² Large numbers of subjects are often needed, even to detect big changes in uveoscleral outflow. This method is more successful at detecting within- and between-group differences in uveoscleral outflow than it is at determining absolute values. Until a noninvasive method is developed to measure uveoscleral outflow directly, mathematical calculation remains the only way to assess uveoscleral outflow in humans.

In animals, uveoscleral outflow can be measured by perfusing a large tracer, such as radioactive albumin or fluoresceinated dextran, into the anterior chamber at a given IOP, and then quantitating the amount of tracer accumulated in the ocular tissues over a specified time period.^{31,32} Methods such as these led to the original discovery of this drainage pathway.

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SECTION III

THE OPTIC NERVE

ANATOMY AND PHYSIOLOGY OF THE OPTIC NERVE

James E. Morgan, M.D. and John C. Morrison, M.D.

Retinal ganglion cell axons traverse the inner retina and converge at the optic nerve head, where they exit the eye and form the intraorbital optic nerve. Abundant evidence suggests that the optic nerve head is the major site of axonal damage in glaucoma. In this region, axons bend through 90 degrees and rearrange to match the topographic organization of the intraorbital portion of the optic nerve. Although the pathophysiology of glaucoma inevitably focuses on changes occurring in axons, the glial cells, connective tissues, and microvasculature of the optic nerve head all play unique, important roles to ensure the health of these axons as they journey from the eye to the brain (see Chapter 10). A detailed understanding of the anatomy and physiology of this region is central to appreciating the pathophysiology of retinal ganglion cell death in glaucoma and its clinically detectable changes.

GENERAL ANATOMY OF THE ANTERIOR OPTIC NERVE

The optic nerve head is traditionally divided into distinct regions, based on their association with the connective tissue lamina cribrosa (Fig. 8–1). The differences among these regions reflect the changing conditions to which the axons are exposed as they pass through the optic nerve head. These differences include axonal myelination just posterior to the lamina cribrosa, distinct arteriolar sources of blood supply, and an abrupt decrease in tissue pressure from the intraocular pressure (IOP) to that of the cerebrospinal fluid. This pressure differential is often exacerbated in glaucoma.

The optic nerve head, visible clinically as the optic disc, forms the point of exit for ganglion cell axons through the scleral canal. The scleral rim (of Elschnig) forms the boundary of this opening, a slightly vertical oval measuring 1.75 mm high and 1.50 mm wide.¹ These dimensions vary considerably among individuals, and

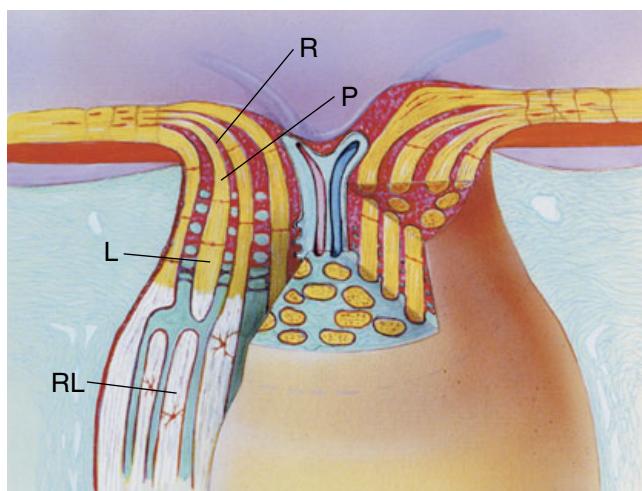


FIGURE 8–1 Representation of the primate optic nerve head, illustrating its organization into four regions: R, retinal nerve fiber layer; P, prelamina; L, lamina cribrosa; RL, retrolamina. (From Kline LB. *Optic Nerve Disorders*. San Francisco: Am Acad Ophthalmol; 1996:1–20, with permission.)

reported axon totals per optic nerve range from 777,000 to as high as 1,679,000.²

The anterior part of the optic nerve comprises the axons within the eye to their junction with the myelinated portion of the nerve. This is typically divided into four regions, with some variation in nomenclature (Table 8–1).

RETINAL NERVE FIBER LAYER

Optic nerve axons originate from the ganglion cells of the inner retina. In keeping with the precise retinotopic organization of the retina, these axons run with fibers that arise from neighboring cells in bundles, formed by Müller's cell processes.^{3,4} However, some axons pass between bundles as they approach the optic disc.^{5,6}

TABLE 8-1 REGIONS OF THE ANTERIOR OPTIC NERVE

Region	Prominent Features
Retinal nerve fiber layer	Unmyelinated ganglion cell axons converge on the optic nerve head
Prelamina (choroidal lamina)	Axons segregate into bundles and begin to turn into the optic nerve head Bundles separated and supported by astrocyte processes
Lamina cribrosa (scleral lamina)	Connective tissue sheets with holes aligned to transmit the axonal bundles at the level of the posterior sclera Astrocyte processes support axons with intimate contacts within the axonal bundles
Retrolaminar optic nerve (intraorbital, myelinated optic nerve)	Myelination begins at the posterior limit of the lamina cribrosa

Axon bundles in the retinal nerve fiber layer course toward the optic nerve head in three zones: the papillomacular bundle, nasal radial bundles, and the relatively thick arcuate bundles. Chapters 12 and 13 illustrate these bundles and discuss their relationship to glaucomatous optic nerve damage and how they result in the characteristic arcuate scotomata and nasal steps of the glaucomatous visual field. Chapter 12 discusses methods of measuring and assessing the thickness of the nerve fiber layer.⁷⁻⁹

The vertical organization of ganglion cell axons within the retinal nerve fiber layer and into the myelinated optic nerve remains controversial. In general, fibers from peripheral regions of the retina occupy the peripheral portions of the optic nerve, whereas the more “proximal” axons lie centrally.^{10,11} Some studies suggest that axons from peripheral ganglion cells lie deep in the nerve fiber layer, and axons from more centrally located cells pass through them to occupy the more superficial parts of the nerve fiber layer.^{3,9-12} In this scheme, axons would enter the optic nerve head already matched to their eventual organization in the retrobulbar optic nerve.

Other studies indicate that peripheral fibers lie superficial to axons arising from more centrally located cells.^{14,15} This implies that nerve fibers must reorganize in a complex fashion as they enter the optic nerve head in order to comply with their ultimate positions in the optic nerve. However, axonal organization in the retina may be relatively coarse,⁵ with peripheral axons scattered throughout the nerve fiber layer. Similarly, the central–peripheral organization of axons in the optic nerve may be less precise than previously thought.¹⁶

CONTROVERSY

Some studies report that ganglion cell axons are precisely organized within the retinal nerve fiber layer, depending on the proximity of their cell bodies to the optic nerve head. Others suggest that peripheral axons are scattered throughout the nerve fiber layer.

Retinal glial cells surround axons as they leave the retinal ganglion cell body and contribute significantly to axon organization in the nerve fiber layer.¹⁷ The axons are separated into bundles by the processes of Müller glial cells, whose endfeet, together with the less numerous astrocytes, form the internal limiting membrane between the retina and vitreous.¹⁸ It is likely that processes from both the astrocytes¹⁸ and the Müller cells underlie the striations seen in the healthy nerve fiber layer under red free illumination.⁹

PRELAMINAR OPTIC NERVE (CHOROIDAL LAMINA)

As nerve fibers turn into the optic nerve, their segregation into nerve fiber bundles continues. This is accomplished by the processes of astrocytes that surround the nerve bundles and intertwine with each other to form a basketlike arrangement.¹⁹ Longitudinal, histologic sections of this portion of the optic nerve demonstrate vertical stacks of astrocyte cell bodies, effectively forming glial tubes that merge with connective tissue stacks of the lamina cribrosa.^{20,21}

Glial cells also send numerous processes into the nerve fiber bundles, maintaining intimate contact with individual axons.¹⁹ Through these associations, astrocytes probably help maintain the appropriate extracellular environment for the axons, which are metabolically very active as they conduct action potentials. At the margin of the nerve, axons are separated from the choroid and the sclera by a band of astrocytes known as the border tissue of Jacoby. More anteriorly, astrocytes form the intermediary tissue of Kuhnt, which provides a barrier between the axons and the terminal layers of the retina (Fig. 8-2).

LAMINA CRIBROSA (SCLERAL LAMINA)

The main physical support for axons appears at the level of the sclera, in the form of approximately 10 connective-tissue sheets.^{20,21} These sheets, the scleral lamina cribrosa, span the scleral opening at the back of the eye, inserting into the outer half of the sclera. Each of these sheets, or plates, contains openings, or pores, that are in approximate

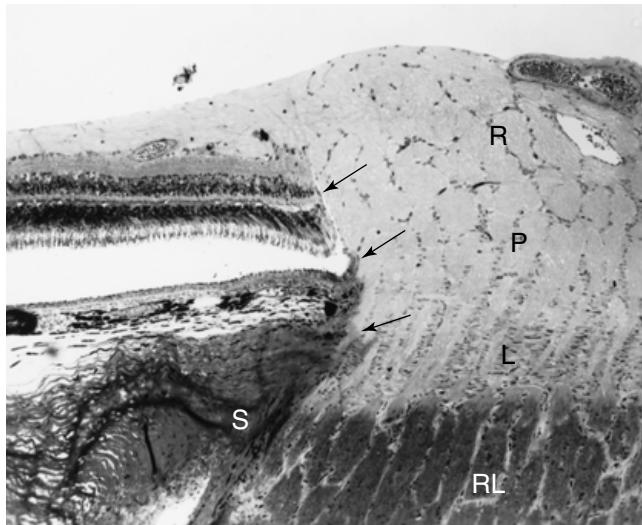


FIGURE 8-2 Longitudinal histologic section of the human optic nerve head demonstrating the different regions, as indicated in Figure 8-1. Arrows indicate the glial border of Kuhnt and the more posterior intermediary tissue of Jacoby. R, retinal nerve fiber layer; P, prelamina; L, lamina cribrosa; RL, retrolamina; S, sclera. Note the onset of myelination at the posterior border of the lamina cribrosa. (Courtesy of Mark O. M. Tso, M.D.)

vertical alignment to allow nerve fiber bundles to pass into the retrolaminar optic nerve. The number of pores increases by approximately 50% from the choroidal to the scleral lamina.²²

Histologically, the anterior portion of the sclera projects slightly anterior and into the optic nerve head, forming a shelf beneath which the connective tissue laminar sheets project (see Fig. 8-2). The glial border of Jacoby separates the sclera from the nerve bundles at this level and the choroidal lamina. Tight junctions between these cells and those of the intermediary tissue of Kuhnt help form a partial blood–brain barrier, isolating the microenvironment of the laminar and prelaminar optic nerve from that of the adjacent sclera, choroid, and retina.²³

In humans, the pores of the lamina cribrosa are larger and fewer, and the laminar beams thinner, in the superior and inferior poles of the optic nerve head. (Fig. 8-3).²⁴ Given that axon loss occurs preferentially at the superior and inferior poles of the optic disc, these observations, and the fact that block of axoplasmic transport occurs at the level of the lamina cribrosa, suggest that the laminar beams influence glaucomatous nerve fiber damage through potential mechanisms that are discussed in Chapter 10.

PEARL... The unique structure of the lamina cribrosa, combined with the characteristic pattern of glaucomatous optic nerve damage, suggests that the laminar beams influence nerve fiber damage in glaucoma.

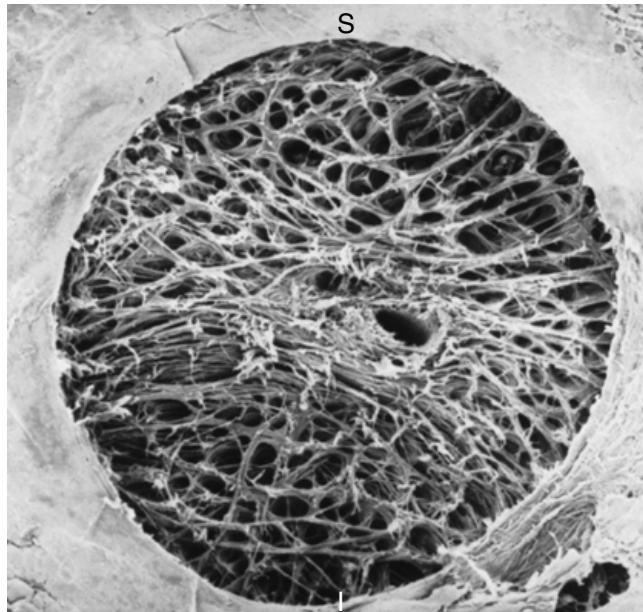


FIGURE 8-3 Scanning electron microscopic analysis of a normal human optic nerve head following trypsin digestion. Note thinner, less dense laminar beams in the superior (S) and inferior (I) regions of the nerve head. (Courtesy of Harry Quigley, M.D.)

Because the number of pores increases with increasing depth in the nerve, axons probably do not take a direct path out of the eye, particularly in the thicker disc periphery.^{25,26} This may increase the susceptibility of these axons to damage from increased IOP.²⁶

The composition of the lamina cribrosa governs its physical behavior and affects axonal damage in glaucoma. In adults, the cores of the laminar beams possess large amounts of interstitial type I collagen, which imparts strength and resistance to deformation (Fig. 8-4). Laminar beams also show some resilience and elastic behavior due to the presence of type III collagen and abundant elastin fibrils.^{27–31} This combination of supportive and elastic properties suggests that all components of the lamina cribrosa play a complex role in protecting ganglion cell axons from chronic and fluctuating IOP.

In addition, the core of the laminar beam is surrounded by basement membranes derived from and maintained by astrocytes. This basement membrane includes laminin, collagen type IV, fibronectin, and heparan sulfate-containing proteoglycan.^{32,33} These astrocytes provide an interface between the laminar beams and nerve fiber bundles,²¹ and often extend into the core of the laminar beams, suggesting that astrocytes also help maintain cribriform structure. Other basement membranes are deposited by the endothelial cells of capillaries contained within the laminar beams.

The structure of the lamina cribrosa changes with age. As the number of axons decreases,³⁴ the size of the laminar pores also decreases. This is accompanied by an increase in

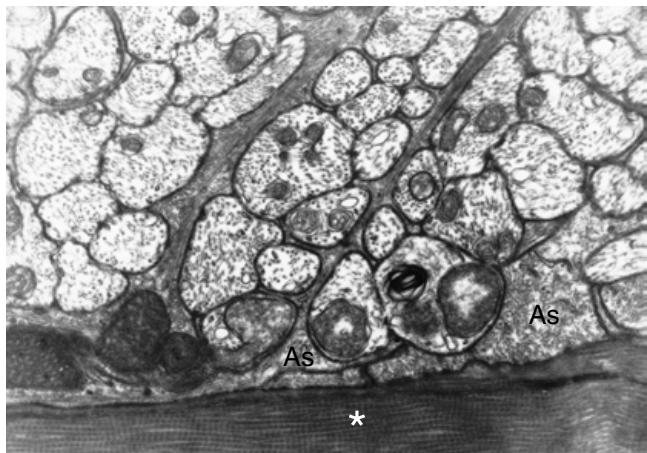


FIGURE 8-4 Transmission electron micrograph of the primate lamina cribrosa. Note collagenous laminar beam (*) with adjacent glial astrocytes (As). Lighter ganglion cell axons are cut in cross section and are intimately related to darker astrocyte processes that extend into the axon bundles. (From Kline LB. *Optic Nerve Disorders*. San Francisco: American Academy of Ophthalmology; 1996:1–20, with permission.)

the amount of interporc connective tissue²² due to continuous production of various collagens in the core of the beams.³⁵ Elastin fibers also thicken with age, possibly due to cross linking and aggregation rather than new synthesis.³⁵ The resulting elastosis,³⁶ along with changes in the composition of proteoglycans,³⁷ may reduce tissue elasticity.

Although the supportive connective tissues have long been synonymous with the lamina cribrosa, the astrocytes lining the laminar beams are an equally important but poorly understood feature of the normal optic nerve head. At this level, astrocytes are interconnected via gap junctions,³⁸ and they send numerous processes into the nerve fiber bundles to form secondary projections that intimately contact the still unmyelinated axons (see Fig. 8-4). Through these contacts, astrocytes provide metabolic support for axons and supply the anatomic connections that allow the laminar beams to influence axonal function and survival.

SPECIAL CONSIDERATION

Astrocytes lining the laminar beams are an important, though poorly understood, feature of the normal optic nerve head.

RETROLAMINAR OPTIC NERVE (INTRAORBITAL, MYELINATED OPTIC NERVE)

The retrolaminar optic nerve marks the posterior border of the lamina cribrosa and the beginning of axonal myelination. At this junction, posterior laminar beams blend into

the connective tissues, or septae, of the retrolaminar optic nerve. In general, the optic nerve septa run parallel to the nerve fiber bundles and consist of a mixture of interstitial and fibrillar collagen, elastin, and proteoglycans. This composition is similar to that of the laminar beams, but less compact. These septa are also lined with glial cells and basement membranes and contain capillaries.

In the optic nerve, glial cells are predominantly oligodendroglia, which form myelin sheaths that encase the axons in their passage to the lateral geniculate nucleus. Astrocytes continue to play an important role, however, because they contact axons at the nodes of Ranvier, where they help maintain the extracellular environment necessary to propagate action potentials. At the nerve periphery, axon bundles are separated from the meningeal sheath by several layers of thick-bodied astrocytes that form a limiting glial membrane called Graefe's peripheral layer.¹⁹

BLOOD SUPPLY TO THE ANTERIOR OPTIC NERVE

ANATOMY

The entire blood supply to the eye is derived from the ophthalmic artery, a branch of the internal carotid artery (Fig. 3-2A). Shortly after entering the orbit, the ophthalmic artery gives rise to the central retinal artery and two posterior ciliary arteries. The central retinal artery enters the ventral aspect of the optic nerve 5 to 15 mm behind the eye. The posterior ciliary arteries travel forward on either side of the optic nerve and, at the junction of the nerve and globe, they give rise to 15 to 20 (paraoptic) short posterior ciliary arteries and two long posterior ciliary arteries. Short posterior ciliary arteries enter the sclera in a ring around the nerve, whereas the long posterior ciliary arteries enter the sclera nasally and temporally to the optic nerve and travel in the horizontal plane within the suprachoroidal space toward the anterior segment. Here they join perforating branches of the anterior ciliary arteries to supply the iris and ciliary body.

The retrolaminar optic nerve receives blood from two sources relative to the entry of the central retinal artery (Fig. 8-5).³⁹ Proximal to this entry site, the blood supply is entirely centripetal, from pial vessels in the meningeal sheath that surrounds the nerve. After it enters the optic nerve, the central retinal artery supplies intraneuronal arterioles, which anastomose with the pial vessels to serve optic nerve capillaries up to the lamina cribrosa. Additional supply also comes from direct choroidal arteries.⁴⁰

From the posterior border of the scleral lamina to the retinal nerve fiber layer, the central retinal artery makes no contribution to the circulation of the optic nerve head. The scleral lamina, choroidal lamina, and deeper parts of the nerve fiber layer are supplied by a rich anastomosis of

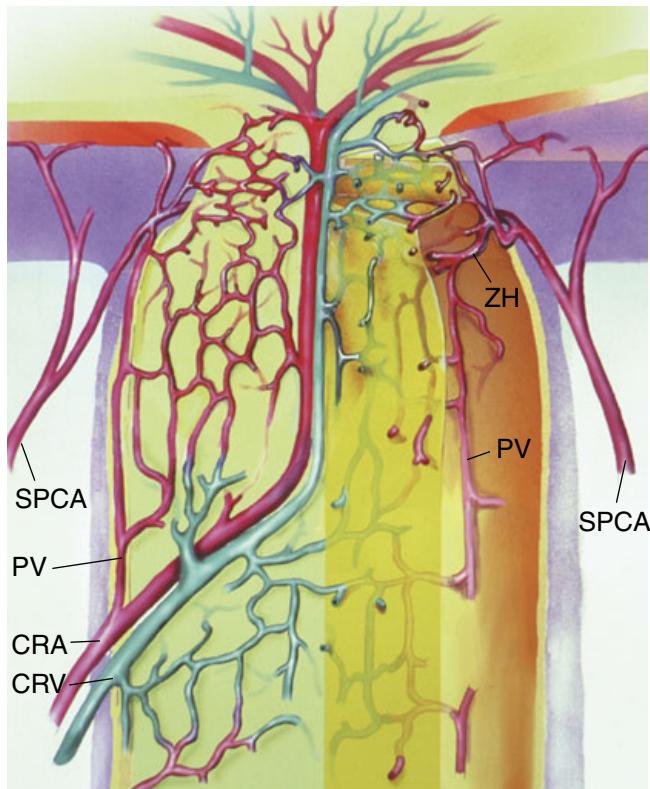


FIGURE 8-5 Schematic representation of the microvascular blood supply to the optic nerve and nerve head: CRA, central retinal artery; CRV, central retinal vein; SPCA, short posterior ciliary arteries; ZH, circle of Zinn-Haller; PV, pial vessels. (From Kline LB. *Optic Nerve Disorders*. San Francisco: American Academy of Ophthalmology; 1996:1–20, with permission.)

vessels derived from branches of the short posterior ciliary arteries (Table 8-2). Because these are end-arteries, it has been suggested that their distribution in the margins of the optic disc may indicate areas at risk for ischemic damage.⁴¹

TABLE 8-2 BLOOD SUPPLY TO THE ANTERIOR OPTIC NERVE BY REGION

Region	Source and Route
Retinal nerve fiber layer	Central retinal artery Retinal artery branches and peripapillary nerve fiber layer
Prelamina	Posterior ciliary arteries Circle of Zinn Haller Occasional choroidal arteriolar branches
Lamina cribrosa	Posterior ciliary arteries Circle of Zinn Haller Occasional choroidal arteriolar branches
Retrolaminar optic nerve	Central retinal artery Pial vessels Intraneuronal vessels Posterior ciliary arteries (circle of Zinn Haller) Recurrent pial arterioles

PEARL... The bulk of blood supply to the optic nerve head consists of centripetal flow from the short posterior ciliary arteries, with the central retinal artery providing blood to only the nerve fiber layer and some of the retrolaminar optic nerve.

The most famous of these anastomoses is the so-called circle of Zinn Haller (Figs. 8-5; 8-6A, B). This is a microscopic, intrascleral arteriole usually derived from short posterior ciliary arteries that enter the sclera nasal and temporal to the optic nerve. These vessels arch above and below the optic nerve and form a horizontal ellipse around it. This anastomosis is quite distinct from a macroscopic extrascleral anastomosis composed of short posterior ciliary arteries at the superior aspect of the nerve before they enter the sclera.⁴² The Zinn Haller circle is highly variable. Although reported as intact 77% of the time in one series, significant narrowing occurred at various locations.⁴³

Arterioles from the circle of Zinn Haller provide a substantial part of the blood supply to the scleral lamina (see Fig. 8-6A). The circle also serves the adjacent choroid, as well as branches that contribute to the pial circulation and the retrolaminar optic nerve. Other branches extend to recurrent choroidal arterioles derived from the Zinn Haller circle.⁴² Anteriorly, the short posterior ciliary arteries supply the anterior optic nerve head as well as the peripapillary choroid.⁴⁴ Although choroidal arterioles can supply small branches to the capillaries of the optic nerve head, direct communication from the choriocapillaris is rare. Some reports suggest that some of the short posterior ciliary arteries run through the sclera and border tissue of Elschnig to supply the prelaminar part of the optic nerve.⁴⁵

The central retinal artery supplies the optic nerve head only at the level of the superficial retinal nerve fiber layer. This occurs via a fine network of capillaries that branch off retinal arterioles to anastomose with capillaries from the short posterior ciliary vessels. Additional supply comes from cilioretinal arteries, when they are present.

Capillaries of the optic nerve head, derived from all of the above arterial sources, form a continuous network that extends from the nerve fiber layer to the retrobulbar optic nerve (see Fig. 8-6B). They consist, primarily, of vascular endothelium, basement membranes, and pericytes. As with other vessels of the central nervous system, their endothelial cells are nonfenestrated, nonleaky, and constitute the blood-brain barrier. The pericytes may contribute to the regulation of vascular caliber and the local control of tissue perfusion. All incoming vessels are surrounded by a dense network of astrocytes.

At the level of the nerve fiber layer and the choroidal lamina cribrosa, these capillaries lie within and between the nerve fiber bundles, in close association with astrocyte

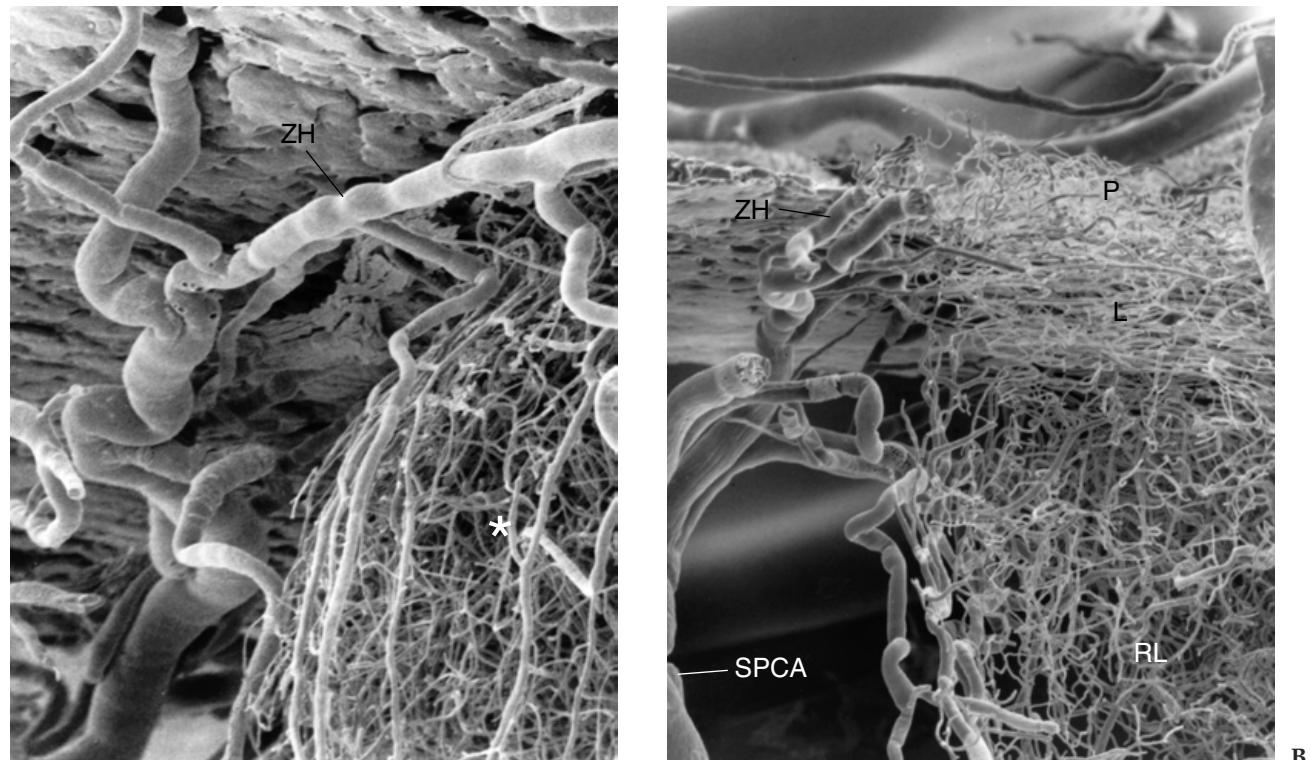


FIGURE 8-6 Methylmethacrylate castings of the human optic nerve microvasculature as viewed by scanning electron microscopy. (A) Circle of Zinn Haller (ZH) supplying capillary bed of the optic nerve head (*). (B) Continuous capillary bed throughout the optic nerve head. Note circle of Zinn-Haller (ZH) and short posterior ciliary arteries (SPCA). P, prelamina; L, lamina cribrosa; RL, retrolamina. (From Onda E, Cioffi G, Bacon DR, and Van Buskirk EM. Microvasculature of the human optic nerve. *Am J Ophthalmol* 1995;120:92–102, with permission.)

columns. In the scleral lamina cribrosa, capillaries are encased by the laminar beams and are arranged in several layers that encircle the axonal bundles. Capillaries of the intraorbital optic nerve lie within the connective tissue septae.

In contrast to the arterial supply, venous drainage from the optic nerve is relatively simple (Fig. 8-5). At all levels, the optic nerve head drains primarily into the central retinal vein, situated within the optic nerve head adjacent and lateral to the central retinal artery, often sharing a common adventitial sheath. The more anterior regions of the optic nerve head drain into the retinal veins, which join to form the central retinal vein. More posteriorly, venous blood drains either directly into the central retinal vein or into one of its tributaries.

SPECIAL CONSIDERATION

Venous return from all levels of the optic nerve head empties into the central retinal vein. This has important implications for the development of vascular occlusion, particularly in eyes with advanced glaucomatous optic nerve damage.

MICROVASCULAR PHYSIOLOGY OF THE OPTIC NERVE

Most anatomic studies of the optic nerve head microvasculature suggest that a continuous capillary bed connects all levels of the nerve, providing potential collateral flow from one region to another. However, the response of these different tissue beds to specific physiological stimuli can be quite distinct, and perfusion of the deeper, laminar regions of the nerve head may differ from that of the superficial nerve head and retina. Although complex, the control of blood flow in the optic nerve may contribute in some manner to the pathophysiology of glaucoma.

Blood flow in any vascular bed is determined mostly by the size of the vessels, which results from the tone of musculature in their vessel walls. As with all vessels in the central nervous system, the microvasculature of the optic nerve head, whether derived from the central retinal artery or the posterior ciliary arteries, is capable of autoregulation. This is the ability of blood vessels to respond to local stimuli and maintain constant perfusion in the face of changing physiological conditions. For example, in systemic hypertension, vessels constrict, whereas they dilate with reduced O_2 or elevated CO_2 .

In the eye, this vascular regulation is remarkably effective. It responds to the metabolic demands of the retina,⁴⁶

TABLE 8-3 MECHANISMS OF AUTOREGULATION

Neurogenic (extraocular autonomic nerves)
Monitoring of small molecules and ions
Mechanoreceptors
Vasoactive factors
Nitric oxide (vasodilation)
Endothelin (vasoconstriction)
Systemic humoral factors (renin-angiotensin, adrenalin)

adjusting to variations in neuronal function, and can mediate vasodilation when confronted with increased IOP to ensure perfusion of the optic nerve head. This system has a large dynamic range and helps maintain adequate blood flow, even if the IOP exceeds 40 mm Hg (Table 8-3).⁴⁷

Neurogenic control of vascular tone may be important in the regulation of optic nerve head perfusion in the extraocular portion of the optic nerve and the short posterior ciliary arteries, which possess a rich plexus of autonomic nerves. However, neither the retina nor the prelaminar optic nerve receives a similar input. These nerves secrete a number of vasoactive molecules, such as nora-drenalin (NA), acetylcholine, nitric oxide (NO), and substance P. They may also exert some control over local vascular tone given that alpha and beta adrenergic receptors have been found in retinal and posterior ciliary vessels.

Local vascular autoregulation operates in response to two principle stimuli.⁴⁸ First, it maintains the proper concentration of molecules and ions essential for neuronal function, such as O₂, CO₂, K⁺, and pH. Of these, O₂ is most important in detecting reduced blood flow, probably through the production of prostaglandins and, possibly, the vasodilator, adenosine.⁴⁹ Second, blood vessels can respond to mechanoreceptors through a Ca⁺⁺-dependent mechanism in the vessel wall, constricting as the blood pressure increases, which stretches the vessel wall, and dilating as it falls.

Endothelial cells lining the internal vessel wall also help regulate vascular tone. They release a number of vasoactive factors, of which NO is the principal vasodilating agent. In short posterior ciliary arteries (SPCAs), NO appears likely to maintain a basal tone because blockage of its production results in vasoconstriction of these vessels.⁵⁰ In addition, damage to the endothelium in hypertension⁵¹ and ischemia can result in reduced production of NO with consequent reduction in vascular caliber.

Vasoconstriction is also mediated in part by the family of endothelin polypeptides. Of these, endothelin-1 is probably the most important. By acting on receptors located on the endothelial cells and the smooth muscle of the blood vessels, this polypeptide can induce calcium-mediated vasoconstriction sufficient to reduce blood flow in the anterior part of the optic nerve.⁵² The levels of endothelin-1 increase in hypoxia/stress⁵³ and, in ischemic conditions, can lead to vasospasm.⁵⁴

However, the actions of the endothelins are not simple. Endothelin-1 increases blood flow at low doses and

reduces flow at higher doses, possibly through unique effects on different receptor subtypes.⁵⁵ In the venous circulation, endothelins tend to cause constriction, although the importance of venous regulation in the human eye is still unknown.

Finally, systemic humoral factors will also influence the control of blood supply. The renin angiotension system may be involved given that angiotensin II can reduce optic nerve head perfusion.⁵⁶ Adrenalin can both constrict vessels via alpha receptor stimulation and dilate vessels via beta receptors. However, the precise roles of these agents in the day-to-day regulation of optic nerve head blood flow are unclear.

Considering the wide range of vasoactive substances, it is difficult to determine which may be the most important. Studies have suggested a role for endothelin because its levels may be increased in low tension and possibly open-angle glaucoma (OAG).⁵⁷⁻⁵⁹ The finding that nitric oxide synthase (NOS) expression is increased in OAG may also suggest a role for nitric oxide.⁶⁰

OPTIC NERVE AXON PHYSIOLOGY

Optic nerve axons are not passive wires threaded through the complex layers of the optic nerve head. They must conduct action potentials, maintain their structure, and ensure the continued well-being of their cell of origin, the retinal ganglion cells.

Like all neurons, ganglion cells must have a mechanism for the cell body to stay informed of conditions along the axon and at the synapse, and maintain the size and functional properties of the axon.⁶¹⁻⁶³ This is accomplished through axonal transport, a complex, energy-dependent process that moves molecules away from (anterograde or orthograde) and toward (retrograde) the cell body.

Both orthograde and retrograde transport rely on the axonal cytoskeleton, which is composed of microtubules, neurofilaments, and microfilaments.⁶⁴ Microtubules and neurofilaments, which measure about 10 to 100 μm in length, are oriented parallel to the long axis of the axon (Fig. 8-7).

Microtubules lie in bundles within the neurofilaments, along with surrounding globular proteins, many of which appear to be attached directly to microfilaments, which appear to help organize the microtubule matrix. Side arms composed of microtubule-associated proteins may also help link microtubules to neighboring microfilaments and neurofilaments. Neurofilaments also have side arms that aid slow axonal transport and allow interaction with neighboring neurofilaments and microtubules.

Slow axonal transport often segregates into two waves that travel at different velocities: SCa and SCb (Table 8-4).⁶⁵ The SCa wave appears to consist primarily of proteins closely associated with neurofilaments and microtubules. The SCb wave contains many more proteins including actin (associated with microfilaments) and tubulin. Although the actual mechanism is not completely understood, slow

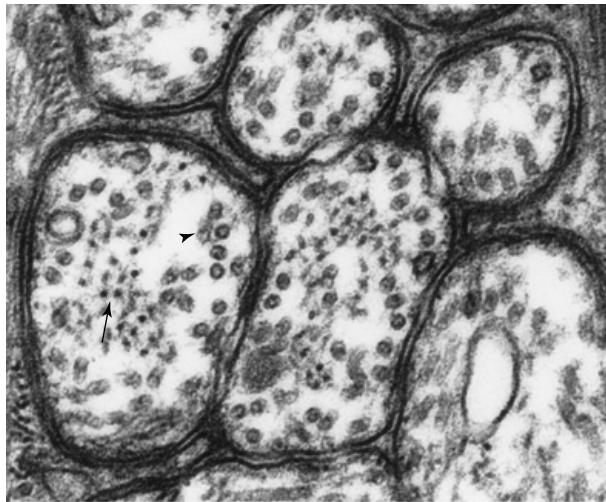


FIGURE 8-7 Transmission electron micrograph of ganglion cell axons cut in cross-section within the optic nerve head, demonstrating neurofilaments (arrow) and microtubules (arrowhead).

axonal transport appears to represent the movement of neurofilaments and microtubules down the axon, and thus helps maintain its integrity and caliber.

In contrast, fast axonal transport travels from 20 to 400 mm per day.^{62,63} Orthograde transport conveys membrane-bound vesicles, such as synaptic vesicles and plasma membrane components, to the distal axon. Retrograde transport moves lysosomes, pinocytic vesicles, and degraded multivesiculate bodies toward the cell body. Mitochondria can apparently move in either direction.

Fast axonal transport appears to occur in close association with microtubules and requires adenosine triphosphate (ATP). Because fast transport can proceed in either direction along a single microtubule,⁶⁶ orthograde and retrograde axonal transport are thought to rely on distinct “motor proteins.” One such protein, kinesin, is associated with axonal transport along microtubules away from the cell body (orthograde),^{67,68} whereas another motor protein, dynein, or microtubule-associated protein 1C (MAP-1C), appears to catalyze vesicle movement toward the cell body (retrograde).⁶⁹

TABLE 8-4 AXONAL TRANSPORT

Type	Rate (mm/day)	Rate (mm/day)	Purpose
Slow	1 (Sca)		Move proteins associated with neurofilaments and microtubules down the axon, away from cell body
	2 (SCb)		
Fast	20–400		
Orthograde (kinesin)			Move membrane-bound vesicles and mitochondria away from the cell body
Retrograde (dyenin)			Move lysosomes, pinocytotic vesicles, and multivesiculate bodies toward the cell body

PEARL... Fast axonal transport occurs in close association with microtubules and can proceed in either direction.

Many studies have shown that acutely elevated IOP can inhibit both orthograde and retrograde transport.^{70–75} Similarly, chronic IOP elevation in monkeys^{76,77} and glaucoma in humans⁷⁸ can disrupt axoplasmic flow, leading to a visible buildup of mitochondria and organelles, primarily at the level of the lamina cribrosa.

Disruption of axoplasmic transport may lead to axonal and ganglion cell death in glaucoma, possibly by interrupting the orthograde transport of material necessary to maintain the distal axon and synapse. Alternatively, block of retrograde transport may diminish the delivery of feedback or trophic factors needed to maintain the neuron.

Ischemia, physical compression, and toxins can all affect axonal transport, and it is uncertain which of these are active in glaucoma. Because of this, the exact role of altered axoplasmic transport in glaucomatous optic nerve damage remains unknown.

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CLINICAL EVALUATION OF THE OPTIC NERVE HEAD

Mamdouh Nakla, M.D. and Joseph Caprioli, M.D.

Accurate clinical evaluation of the optic nerve head remains a critical part of glaucoma management. Several examination techniques are available (Table 9-1), and their relative advantages vary with the clinical situation. Because of this, the clinician must be familiar with several methods and be able to extrapolate the findings from one to the other. Understanding the features of the normal optic disc is essential for accurate detection of glaucomatous optic nerve damage.

EXAMINATION TECHNIQUES

DIRECT OPHTHALMOSCOPY

The direct ophthalmoscope is portable, relatively inexpensive, and widely used by nearly all physicians. Its upright image provides approximately 15X magnification and it is

useful for screening populations for glaucoma. It is particularly useful for rapid, undilated follow-up examinations and can reveal nerve-fiber-layer hemorrhages and major changes in the optic disc. In addition, when the scope is held 17 mm in front of the cornea, the small (5 degree) aperture will project a 1.5 mm diameter spot of light on the retina in phakic patients.¹ This provides a reference for determining the size of the optic disc that is independent of refractive error and axial magnification. Good patient fixation, along with use of the small spot to limit distracting reflexes from the edge of the pupil and minimize photophobia, is the key to providing a good view of the nerve head.

Unfortunately, it is often difficult to visualize the optic nerve head with the direct ophthalmoscope through a cataract. In addition, its two-dimensional image may not accurately convey the surface contour of the neural rim. However, by scanning the smallest possible beam

TABLE 9-1 METHODS FOR EXAMINING THE OPTIC DISC

Method	Advantages	Disadvantages
Direct ophthalmoscopy	High magnification Portable Available	Not stereoscopic
Binocular indirect ophthalmoscopy		Low magnification Diffuse illumination
Slit-lamp techniques		
Goldmann, Zeiss lenses	Upright, direct image No air–cornea interface	Inconvenient (Goldmann)
90D and 78D lenses	Convenient Good stereopsis	Virtual, inverted image Air–cornea interface
Hruby lenses	Good stereopsis	Air–cornea interface Requires cooperative patient

across the disc rim, the deflection and movement of the resulting shadows can provide clues to the three-dimensional contour of the optic nerve head. Frequent comparison with stereoscopic methods helps the clinician learn this technique.

INDIRECT OPHTHALMOSCOPY

Binocular indirect ophthalmoscopy with the head-mounted biomicroscope is not adequate to visualize the details of the optic nerve head. Because of the diffuse illumination and the small magnification, one relies on color clues rather than topography, and the optic nerve head often appears "better" than it really is. In addition, the stereoscopic base is small, which exaggerates the axial magnification in relation to the angular magnification.

SPECIAL CONSIDERATION

Indirect ophthalmoscopy with the head-mounted biomicroscope is not adequate for visualizing the details of the optic nerve head.

SLIT-LAMP BIOMICROSCOPY

The slit-lamp biomicroscope with hand-held lenses, such as the Goldmann, the Zeiss, the 78D, and the 90D lenses, offers tremendous advantages in evaluating the details of the optic nerve head. When combined with 10X to 16X slit-lamp magnification, the Goldmann contact lens probably provides the best stereoscopic image, which is upright and virtual. Its main disadvantage is the direct contact with the cornea and the need for a viscous fluid-bonding agent that can complicate subsequent fundus examination and photography. The Zeiss 4-mirror lens has similar advantages, but uses only a tear film interface.

Noncontact lenses, such as the 78D and the 90D lenses, also provide excellent stereopsis. Whereas the 78D lens has a higher magnification, the 90D lens is easier to use with a small pupil and provides a wider field of view. The Hruby lens is a 55D slit-lamp-mounted lens that is less convenient.

The best stereoscopic image with any of these lenses is obtained with a dilated pupil. However, in patients who dilate poorly, the examiner can use nonstereoscopic clues, such as vascular patterns crossing the neural rim, "thinning" of the neural rim, and baring of the lamina cribrosa. If the media are clear, these patients often benefit from skillful, direct ophthalmoscopy, which provides greater magnification.

RECORDING TECHNIQUES

CUP-TO-DISC RATIO

The cup-to-disc (C/D) ratio is commonly used to describe the topographic appearance of the optic nerve head. It is often described as a horizontal and vertical measurement. Earlier screening studies have shown that less than 10 to 11% of the population has a C/D ratio of 0.5 or greater.^{2–5} Current stereoscopic quantitative imaging techniques have shown that the average normal horizontal and vertical C/D ratios are 0.5 and 0.42, respectively.⁶ The vertical measurement may be more sensitive in detecting glaucomatous nerve damage.

Estimating the C/D ratio has several disadvantages. First, this ratio varies widely among normal subjects.⁶ Second, a C/D ratio provides limited information about focal neural rim abnormalities, such as thinning, notching, and sloping, which are so important to glaucoma diagnosis and follow-up. Finally, this technique is poorly reproducible. Several studies have shown that there is a large interobserver and intraobserver variability in estimates of the C/D ratio, even among experts.^{7,8}

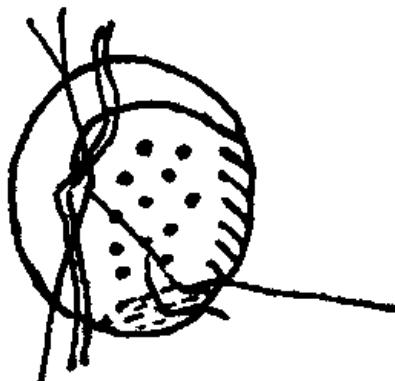
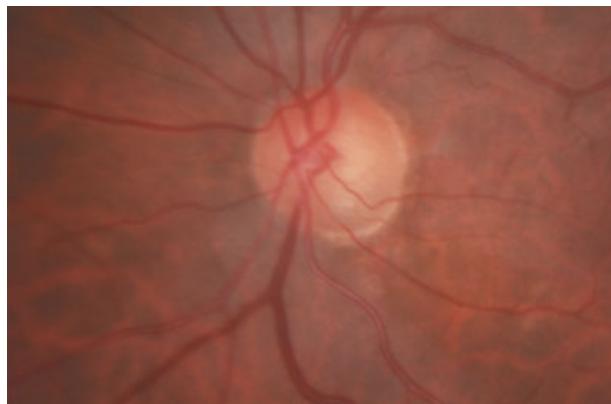
PITFALL... Several studies have shown that there is a large interobserver and intraobserver variability in estimating the cup-to-disc ratio.

DRAWINGS

Shaffer has described techniques for drawing the optic nerve head, which can be next best to a photograph (Fig. 9–1A,B).⁹ When combined with stereoscopic examination, the examiner can draw the many characteristics of the neural rim, such as pallor, sloping, focal thinning and notching, and disc hemorrhages. Other details may also be recorded, including selective vessel details, the degree of exposed laminar architecture, and pits.

DISC PHOTOGRAPHY

Photographs provide permanent records that allow for detailed comparisons of subtle progression of glaucomatous optic nerves that could be easily missed during examination. Photographs are superior to disc drawings for detecting the early signs of progression.¹⁰ Monoscopic and stereoscopic photographs are both useful for detecting glaucoma progression when correlated with visual field measurements.¹¹ However, monoscopic photographs may not be ideal for detecting subtle neural rim and vascular changes.



B

FIGURE 9-1 (A) Optic disc photograph and (B) example of disc drawing. Solid lines represent inner and outer edges of the neural rim, and radiating lines are used to indicate sloping of the neural rim. Dots represent lamina cribrosa.

Stereoscopic disc photography is currently the standard method of monitoring glaucoma patients. These images may be obtained either simultaneously or nonsimultaneously. Nonsimultaneous images can be obtained by having the patient shift fixation, or by shifting the camera position between photographs to obtain the stereoscopic effect. Allen introduced a stereoscopic image separator to permit sequential photographs at a predetermined stereoscopic base.¹² Simultaneous disc photography is performed by fundus cameras that are equipped with prisms to separate the two images. This minimizes image-shift artifact. Careful evaluation of color stereoscopic disc photographs offers the most sensitive currently available technique to demonstrate progressive glaucomatous damage.¹³

THE NORMAL OPTIC NERVE HEAD

DISC RIM

In the normal eye, the inferior neural rim is usually the widest, followed by the superior, nasal, and temporal rims.^{14–16} This is easily remembered by the mnemonic “ISN’T” (Fig. 9–2). The normal neural rim is always intact for 360 degrees, with no areas of rim absence, focal thinning, notching, or hemorrhages. In general, the contours of the superior and inferior rims appear similar.

DISC SIZE AND SYMMETRY

The size of the optic disc varies tremendously in the normal population (Fig. 9–3). It is estimated that disc size may vary from 0.95 to 2.9 mm in the vertical diameter (average 1.85–1.95 mm) and 0.9 to 2.6 mm in the horizontal diameter (average 1.70–1.80 mm).^{17–20} Whereas large optic discs tend to have relatively large

cup-to-disc ratios, their neural area and absolute number of nerve fibers can be normal because the area of the optic disc and the neural rim are correlated.¹⁷

However, disc size is usually symmetrical between the two eyes. In addition, the C/D ratio and neural rim configuration tend to be symmetrical in normal subjects. Armaly²¹ found that fewer than 1% of normal subjects had a difference in C/D ratio of greater than 0.2. In the Framingham study, only 7% of the population exhibited asymmetry of the C/D ratio of greater than 0.1.²² Examining family members can help the clinician assess the differential diagnosis of atypical discs.

SPECIAL CONSIDERATION

The size of the optic disc varies tremendously in the normal population.



FIGURE 9-2 A normal optic disc.

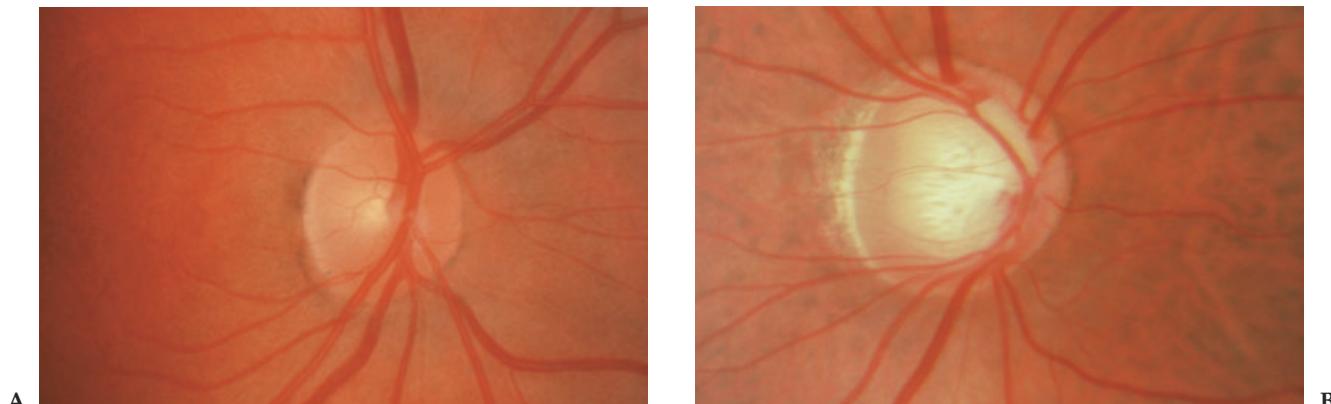


FIGURE 9-3 Right optic discs of two different normal subjects obtained with the same magnification. Note significantly increased cup size in the eye with the larger disc (B), as compared to the smaller disc (A).

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GLAUCOMATOUS OPTIC NEUROPATHY

Mamdouh Nakla, M.D.,
Joseph Caprioli, M.D., and James A. Morgan, M.D.

Accurate clinical recognition of glaucomatous optic neuropathy is important for early diagnosis of the disease and for detecting a change in its status. Many of the characteristic features of glaucomatous optic nerve damage stem from its underlying pathology, dominated by posterior bowing of the scleral lamina cribrosa and dropout of ganglion cell axons. These changes preferentially occur in the superior and inferior regions of the optic nerve head and optic nerve. Although the mechanisms of glaucomatous optic nerve damage are poorly understood, the linkage of pressure and vascular factors with known anatomy and pathology most likely involve the cellular functions of the glial support tissues within the optic nerve head.

The clinical features of glaucomatous optic nerve damage include several forms of progressive neural retinal rim loss, deep focal notching of the rim, optic disc asymmetry, disc hemorrhages, peripapillary atrophy (PPA), and blood vessel changes. Pallor is less specific and should alert the clinician to the possibility of nonglaucomatous optic atrophy.

THE IMPORTANCE OF OPTIC DISC EVALUATION

The examination of the optic disc should complement the information of other clinical measurements. Although intraocular pressure (IOP) is a prominent risk factor for glaucoma, up to one half of all patients with glaucoma can have an initial pressure reading below 21 mm Hg.^{1,2} In addition, only one tenth or fewer of all individuals with elevated IOP develop glaucomatous visual field loss.³⁻⁵

Despite our reliance on automated static threshold perimetry, the development of a reproducible glaucoma-

tous visual field defect is generally more characteristic of moderate to advanced, but not early, disease. Although new, more sensitive psychophysical tests are in progress, their clinical value is still unknown.

Histologically, axon numbers in glaucoma suspects are less than in the optic nerves of normal subjects, and can be as low as 60% of the normal average.⁶ Several studies have shown that progressive disc cupping often precedes the onset of glaucomatous visual field loss,⁷⁻¹² and, on its own, can justify glaucoma treatment.⁹ In ocular hypertensive patients, the cup-to-disc ratio can be very helpful for predicting visual field loss.^{13,14} The ratio of disc change to field change is high in the early stages of glaucomatous damage.¹⁵

PEARL... In early glaucoma, disc changes are more likely than changes in the visual field.

Recognizing glaucomatous cupping also helps the clinician identify glaucomatous versus nonglaucomatous visual field defects. In addition, correlating significant visual field changes with the disc appearance can help distinguish fluctuation from true progression because sensitivity in an individual test location can vary by 20 dB or more over several years.^{16,17}

SPECIAL CONSIDERATION

Correlation with disc appearance can help the clinician determine if significant visual field changes are due to true progression or simple fluctuation.

PATHOLOGY OF GLAUCOMATOUS OPTIC NERVE DAMAGE

One of the most striking and defining pathological features of the glaucomatous optic nerve is the selective loss of nerve fibers in the superior and inferior poles (Fig. 10-1).¹⁸ This generates the characteristic pattern of visual field loss in glaucoma. This selective damage also correlates closely with the structure of the scleral lamina cribrosa, in which the density of laminar beams in the superior and inferior disc is reduced relative to its nasal and temporal regions.^{19,20}

As axons are lost in glaucoma, the laminar pores become more visible and appear more slitlike with respect to the visual axis.²¹ When viewed in longitudinal sections, the plates of the scleral lamina cribrosa appear to rotate posteriorly, hinging at the margin of the scleral rim (Fig. 10-2A,B).²² These changes compress the plates and cause misalignment of the laminar pores.²³

Detailed studies strongly suggest that astrocytes are also altered in the glaucomatous optic nerve head. These cells, which line the lamina cribrosa, using it as a scaffold, are essential for axon survival. At all stages of the disease so far examined, astrocytes appear to become activated.^{24–26} Their cell bodies hypertrophy and they appear to migrate into the axon bundles. They also increase the production of basement membrane (type IV) collagen²⁷ and exhibit de novo expression of elastin.^{28,29} These struc-

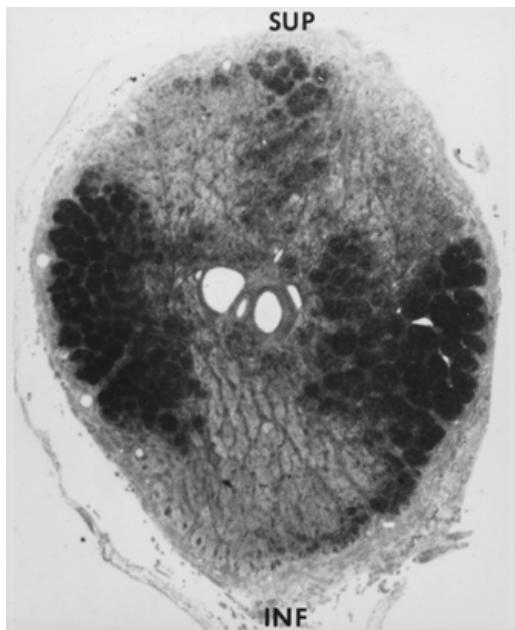


FIGURE 10-1 Cross section of a human optic nerve with glaucomatous optic nerve damage. The pale, atrophic areas illustrate the typical damage to the superior and inferior optic nerve fibers. (Courtesy of Harry Quigley, M.D. Reprinted with permission from Shields, MB. *Textbook of Glaucoma*. 4th ed. Williams and Wilkins; 1998:79.)

tural and functional changes, which appear to be permanent³⁰ and reduce optic nerve head flexibility,³¹ may predispose axons to greater damage.

Histologic studies in human glaucoma and in animal models suggest that the glaucomatous process results in a selective loss of the larger retinal ganglion cells and their axons.^{32–36} This indicates that glaucoma should result in greater damage to cells constituting the magnocellular axonal pathway.^{37,38} This has been supported by studies of the lateral geniculate in glaucoma patients and anterograde tracing experiments in experimental glaucoma.^{39–41} Although the extent of selective damage is currently controversial, this concept has led to several innovative clinical tests, which may help with early glaucoma detection.

Recent studies of cellular morphology in the primate glaucoma model^{42,43} suggest that retinal ganglion cells may shrink prior to their death, similar to shrinkage seen in other forms of neuronal cell death.^{44–46} Whatever the

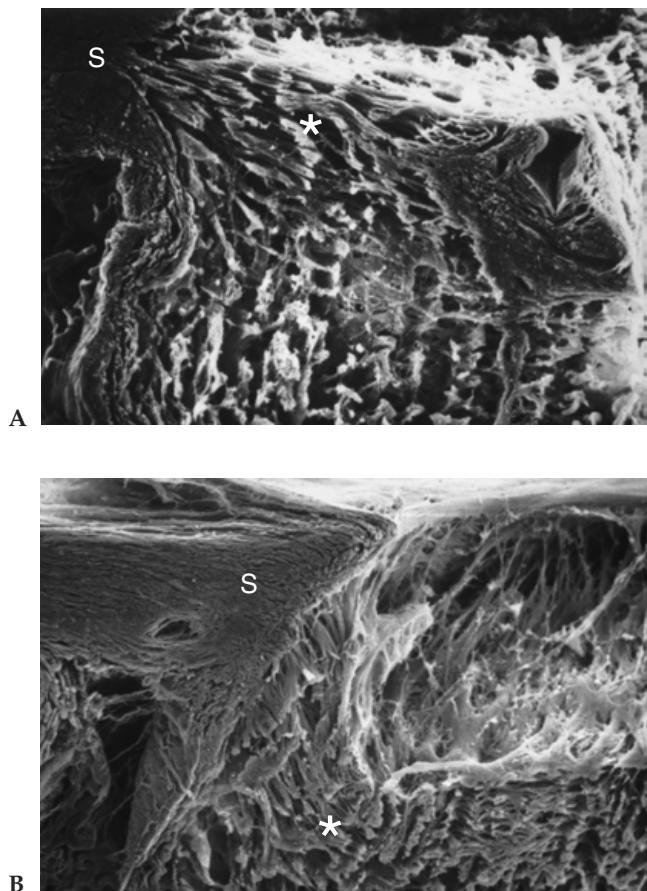


FIGURE 10-2 (A) Scanning electron microscopic study of human optic nerves following trypsin digestion from a normal patient and (B) one with advanced glaucomatous nerve damage. Note compression of the laminar beams (*) and their posterior rotation beneath the scleral rim (S) in (B). (Courtesy of Harry Quigley, M.D. Reprinted with permission from Quigley H, Addicks E, Green W, Maumenee A. Optic nerve damage in human glaucoma, II: the site of injury and susceptibility to damage. *Arch Ophthalmol* 1981;99:635–649.)

underlying process, retinal ganglion cells may be physiologically and morphologically compromised before the final activation of cell death pathways in glaucoma.

MECHANISMS OF GLAUCOMATOUS OPTIC NERVE DAMAGE

Although the importance of eye pressure may vary from patient to patient, there is no question that elevated IOP can produce glaucomatous nerve damage in both humans and monkeys.^{29,47–51} Understanding this process alone is pertinent to the majority of patients with glaucoma.

This disease preferentially damages axons at the vertical poles of the optic disc and is influenced to a variable extent by the level of IOP. Although the actual death of retinal ganglion cells occurs by apoptosis, the events leading up to this event are poorly understood. Conventionally, underlying mechanisms have been grouped into those that cause axon damage through direct mechanical effects within the lamina cribrosa and those mediated by ischemia. These factors likely act synergistically, but discussing them separately helps to clarify their respective roles.

MECHANICAL FACTORS IN GLAUCOMATOUS OPTIC NEUROPATHY

The mechanical theory hypothesizes that, as the plates of the lamina rotate posteriorly with elevated IOP and the pores are increasingly misaligned, axon bundles passing through these pores are damaged, either directly through compression or indirectly through disruption of axoplasmic transport.^{18,52} Retrograde axoplasmic transport is essential for the delivery of many substances, including neurotrophic factors, to the retinal ganglion cell body⁵³ necessary for its survival. Interruptions of this process could trigger pathways that lead to ganglion cell death.⁵⁴

Obstruction of axoplasmic transport at the level of the lamina cribrosa has been demonstrated ultrastructurally in human eyes¹⁸ and in the primate glaucoma model using radioactive tracers (Fig. 10–3).^{52,55,56} Specifically, retrograde transport of neurotrophic factors can be disrupted in experimental glaucoma.⁵⁷

This theory reconciles the characteristic pattern of optic nerve damage in glaucoma with the anatomy of the lamina cribrosa. The regions with the greatest damage correspond to those areas of the lamina cribrosa that have the thinnest laminar beams. They would appear to be less resistant to elevated IOP and would be expected to rotate more easily. However, this theory does not fully explain the cellular mechanisms by which laminar movement causes axonal transport obstruction, particularly since the superior and inferior laminar pores are also larger in these regions, leaving fewer laminar beams available to impinge on the axon bundles.

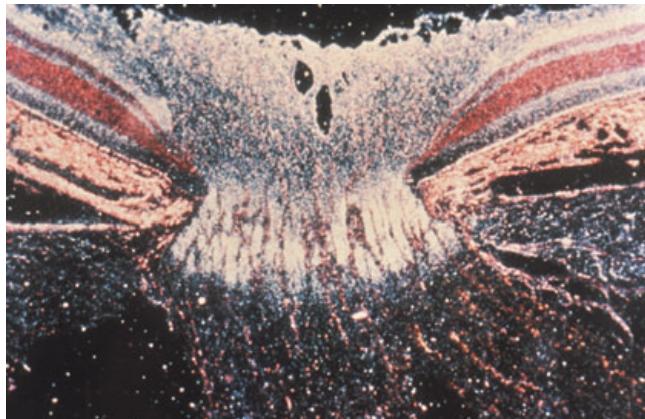


FIGURE 10-3 Autoradiograph of a monkey eye with elevated intraocular pressure following intravitreal injection of tritiated thymidine. Note marked buildup of silver grains (white dots) within the lamina cribrosa, at the level of the sclera. (Courtesy of Mr. E. Barry Davis.)

VASCULAR FACTORS IN GLAUCOMATOUS OPTIC NEUROPATHY

Systemic factors that influence optic nerve head blood flow may also affect glaucomatous damage.^{58–60} The degree of optic nerve damage can be greater in eyes with low perfusion pressure, defined as the difference between systemic blood pressure and IOP.⁶¹ In addition, decreased optic nerve head perfusion can precede the onset of glaucomatous optic nerve damage.⁶² Some studies suggest that glaucoma patients may have faulty optic nerve head blood flow autoregulation.⁶⁰

Blood pressure fluctuation may also be related to damage. Glaucoma-like optic disc cupping has been described in patients following hemodynamic shock,^{63,64} and nocturnal hypotension may decrease optic nerve head perfusion in patients with low-tension glaucoma.^{65,66} Finally, low-tension glaucoma patients tend to have an increased incidence of peripheral vasospasm, as seen in Raynaud's disease,^{67–69} as well as central vasospasm. They can manifest themselves as migraine headaches,⁷⁰ and can also compromise optic nerve head circulation.

However, in spite of these associations, there is no evidence that the frequency of glaucoma is increased in patients with either systemic hypotension or vasospasm. Although IOP and systemic vascular factors can operate independently in some forms of glaucoma,⁷¹ they may also act simultaneously, and their relative importance may vary from one individual to the next.

CELLULAR FACTORS IN GLAUCOMATOUS OPTIC NEUROPATHY

Any theory that integrates these two processes with the observed histologic and clinical features of glaucoma must consider the cells of the lamina cribrosa. This view postulates that the effects of either elevated IOP or reduced

optic nerve head blood flow on axon damage and the structure of the lamina cribrosa are mediated through the astrocytes of the optic nerve head.^{24,25}

Astrocytes and their processes are closely associated with ganglion cell axons, well into the optic nerve.^{72–78} Within the scleral lamina, astrocytes line the laminar beams, separating the axons from the collagenous plates. Through adhesion molecules and basement membrane deposition, they likely contribute to the structural integrity to the optic nerve head.^{27,28} Within the axon bundles, astrocytes maintain intimate contact with the axons themselves, buffering extracellular ion concentrations. In culture, retinal ganglion cell survival depends on the presence of a viable population of astrocytes.⁷⁹

Astrocytes are sensitive to mechanical forces and will alter their function in response to external stress.^{27,28} This altered function could result in active destruction of axons. For example, astrocytes contain nitric oxide synthase, and the inducible form of this enzyme appears to be upregulated in glaucoma.⁸⁰ This might result in increased levels of neurotoxic nitric oxide.⁸¹

Astrocyte dysfunction may also damage axons in a more passive fashion, through a gradual withdrawal of support. In one experimental model, disruption of gap junctions between optic nerve head astrocytes occurs a few days after the increased IOP.⁸² Loss of these junctions, which are widespread in the normal human optic nerve⁸³ and probably help buffer fluctuations of critical ion concentrations in the axon bundles, could be an important step in axonal damage. Changes in astrocyte function could also reduce retrograde axonal transport.

However, this astrocyte hypothesis does not immediately explain the apparent increased susceptibility in the superior and inferior poles of the glaucomatous optic disc. It is possible that, with their reduced number and size in these locations, the laminar beams are less able to protect astrocytes from tensile forces across the lamina. This would increase the likelihood that a given level of IOP could cause astrocyte activation in these regions. Alternatively, less structural support for astrocytes in these locations could make them more vulnerable to the direct effects of IOP and ischemia.

Other cellular factors may also play a role in glaucomatous optic nerve damage. Several studies have reported antibodies against retinal ganglion cells in some glaucoma patients,^{84,85} suggesting that abnormal humoral immunity may contribute to ganglion cell death.⁸⁶ It is currently unclear whether these antibodies initiate or are the result of optic nerve head damage.

Glaucomatous optic neuropathy may also result from damage to retinal ganglion cell bodies occurring outside the optic disc. Short periods of experimental ocular hypertension may adversely affect the ability of Müller cells to remove neurotransmitters, such as glutamate, from the extracellular space.⁸⁷ This could produce increased levels of glutamate, which is selectively neurotoxic to retinal gan-

glion cells, in the vitreous of glaucomatous eyes.⁸⁸ Chapter 38 discusses several potential mechanisms of glaucomatous optic nerve damage in relation to neuroprotection.

CLINICAL FEATURES OF GLAUCOMATOUS OPTIC NEUROPATHY

Specific features of glaucomatous optic nerve damage include changes to the neural rim, and asymmetry between the appearance of the right and left eyes. Vascular changes, peripapillary atrophy and pallor are also associated with glaucoma, but may be less specific.

PROGRESSIVE NEURAL RIM LOSS

Progressive narrowing of the neural rim may follow several patterns. Whereas the cup may enlarge diffusely, the neural rim usually narrows first at the inferior and superior poles of the optic disc. This produces a vertically oval cup, which is often considered a typical sign of glaucomatous damage.⁸⁹ Large normal optic discs, however, may also be slightly oval and can have large cups.

Several patterns of neural rim loss may occur in the same eye. In general, deviation from the "ISNT" rule,^{90–92} or asymmetry between the superior and inferior rim, should alert the clinician to the possibility of glaucomatous optic nerve damage. Focal thinning or notching of the neural rim, particularly at the inferior and superior poles, is a robust sign of glaucomatous damage.⁹³

PEARL... Focal thinning or notching of the neural rim, particularly at the vertical poles, is a robust sign of glaucomatous damage.

Saucerization, where the neural tissue slopes gently from the base of the cup to the disc margin, is common in glaucoma patients (Fig. 10-4). However, this finding can also appear in normal optic nerve heads, and in eyes with



FIGURE 10-4 Optic disc of a patient with normal-tension glaucoma and saucerization of the temporal neural rim.

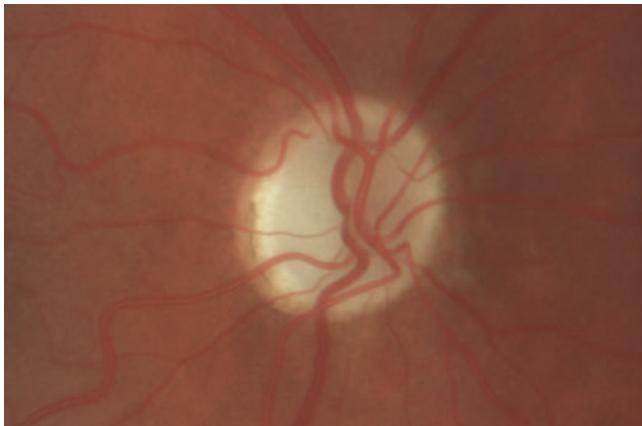


FIGURE 10-5 Temporal neural rim pallor in a patient with a history of anterior ischemic optic neuropathy.

tilted discs, compressive optic neuropathy, and arteritic ischemic optic neuropathy (Fig. 10-5). Careful documentation of the neural rim topography will help identify progression over time.

Cher and Robinson have described “thinning” of the neural rim, in which an intense, narrow slit beam scanned across the disc rim readily penetrates the tissue and illuminates the lamina cribrosa.⁹⁴ This is a soft, but occasionally helpful, sign of early glaucoma.

In end-stage glaucoma, the neural rim may be entirely absent. The cup is deep, with the appearance of a “bean pot.” This is due to posterior bowing of the lamina cribrosa, along with rotation and expansion behind the scleral edge. The vessels often bend sharply at the disc margin, termed bayonetting,⁹⁵ or may disappear at the edge of the cup (Fig. 10-6).

ACQUIRED OPTIC NERVE PIT

Extremely deep, localized focal notching of the neural rim can occasionally resemble a congenital pit. However, these are acquired, and they are not associated with macular

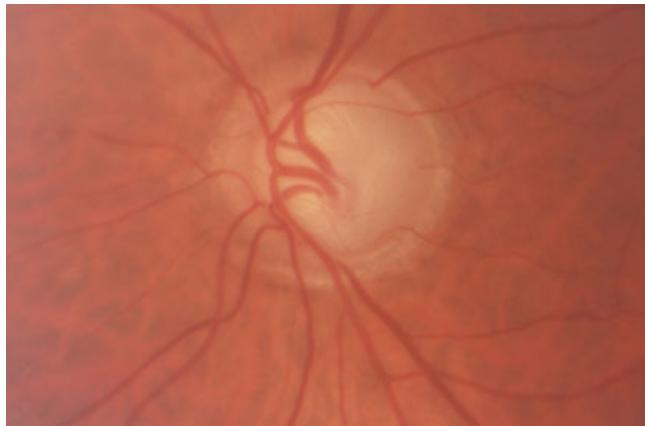


FIGURE 10-6 Severe loss of the neural rim of a patient with advanced glaucoma. Note the sharp bend of the vessels at the superior and inferior edges of the disc. Note also peripapillary atrophy.

abnormalities or congenital disc malformations (Fig. 10-7). Such an “acquired” pit may be more common in primary open-angle glaucoma patients with normal IOPs.⁹⁶

Acquired pits are more often located inferiorly and produce visual field defects close to fixation.⁹⁷ In one longitudinal study, 64% of open-angle glaucoma patients with acquired pits of the optic nerve showed progressive optic disc damage as compared with 12.5% of patients without acquired pits.⁹⁸ Patients with acquired pits were also more likely to have visual field progression and disc hemorrhage.

PEARL... Focal notching of the neural rim may be so deep and localized as to vaguely resemble a congenital pit of the optic nerve head.

DISC ASYMMETRY

Disc asymmetry between the two eyes should also alert the clinician to the possibility of glaucomatous damage. In general, the cup-to-disc ratios of the right and left eyes in a normal subject will not differ by more than 0.2.^{99,100} However, disc asymmetry is not pathognomonic of glaucoma. When studied by computerized image analysis, 30% of glaucoma patients may have a cup volume asymmetry that is greater than the 95th percentile for normal subjects.¹⁰¹

DISC HEMORRHAGE

Disc hemorrhages have been reported in as high as 40% of all glaucoma patients, but tend to be more common in normal-tension glaucoma.^{102,103} These small, flame-shaped, or splinter, hemorrhages usually lie within the peripapillary retinal nerve fiber layer. Although most often located inferotemporally, they can occur in any quadrant (Fig. 10-8).

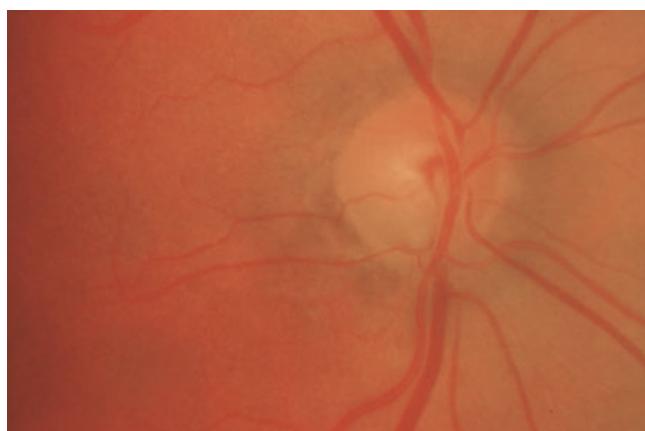


FIGURE 10-7 Acquired pit of the optic nerve at 6 o’clock. Note disappearance of vessels at the edges of the pit.

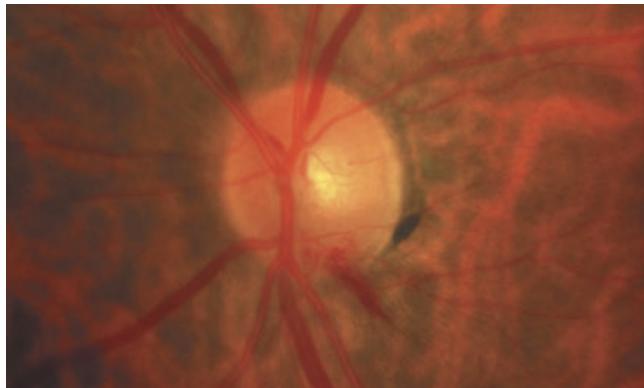


FIGURE 10-8 Typical splinter-shaped disc hemorrhage involving the peripapillary retina.

Disc hemorrhages often precede neural rim notching as well as nerve fiber layer and visual field defects.^{104,105} They often develop at a previously damaged site and can be followed by further excavation of the disc rim (Fig. 10-9A,B). However, they are likely a result rather than the cause of glaucomatous damage. One study found a much higher rate of progressive visual field defects among primary open-angle glaucoma patients with disc hemorrhage than in a matched group of patients without disc hemorrhage.¹⁰⁶ In another, ocular hypertensives with a disc hemorrhage were much more likely to develop field defects.¹⁰⁷ Although hemorrhages are unusual in normal individuals^{103,106} they are not pathognomonic of glaucoma.

PEARL... Disc hemorrhages often precede neural rim notching, and nerve fiber layer and visual field defects.

PERIPAPILLARY ATROPHY

PPA results from misalignment of the edges of the neurosensory retina, retinal pigment epithelium, choroid, and sclera (see Fig. 10-6). In one study, 75% of patients with

progressive optic disc damage had PPA progression, as compared with only 14% of those without progressive disc damage.¹⁰⁸

PPA may also be more likely in normal-tension glaucoma patients (64%) as compared with ocular hypertensives (34%).¹⁰⁹ Some authors suggest that disc damage is more likely adjacent to the area of PPA. However, PPA occurs to a variable degree in most normal eyes and may simply result from degeneration of the choroid and retinal pigment epithelium.¹¹⁰

BLOOD VESSEL CHANGES

As optic nerve damage progresses, disc vessels may shift to reflect changes in the surface of the neural rim. Nasalization, an old term for the nasal displacement of retinal vessels with progressive cupping, is not specific for glaucoma. This may be a normal finding, particularly in eyes with large discs and cups.¹¹¹

Often, with progressive neural rim loss, a vessel that once rested on the neural rim may actually bridge a part of the cup. This is called vessel overpass. With time, this vessel may collapse and hug the cup. “Baring of the circumlinear vessel” refers to vessels that lie in a curved path along the superior and inferior margin of the inner neural rim (Fig. 10-10).¹¹² Baring of the vessel involves the development of a space or pallor between the inner cup edge and the vessel. This may also appear in normal discs, and accurate detection requires careful comparison with previous stereoscopic disc photographs.

Collateral disc, or shunt, vessels may develop in about 3% of otherwise asymptomatic glaucoma patients and ocular hypertensives and may result from small vein occlusions on the disc (Fig. 10-11).^{113,114} It is unclear if this is associated with optic nerve progression.

OPTIC NERVE PALLOR

In normal patients, artificially raised IOP causes pallor of the optic nerve head,¹¹⁵ and patients with acute angle-closure glaucoma can develop pallor of the neural rim,

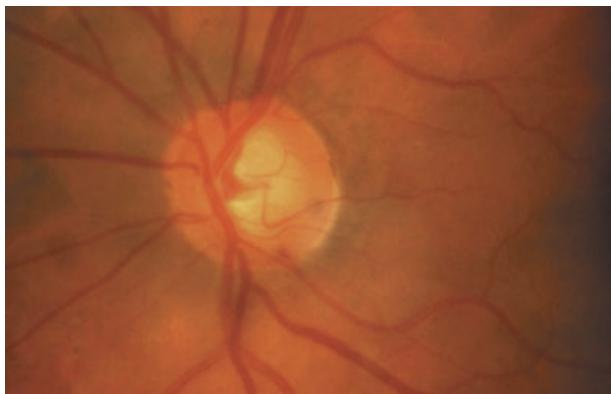
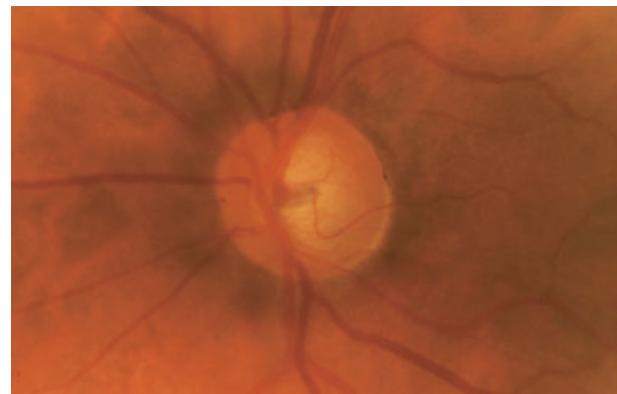


FIGURE 10-9 (A) Small disc hemorrhage at 5 o'clock. (B) This was followed 1 year later by progressive focal thinning of the neural rim, with a corresponding shift in vessel position.



B

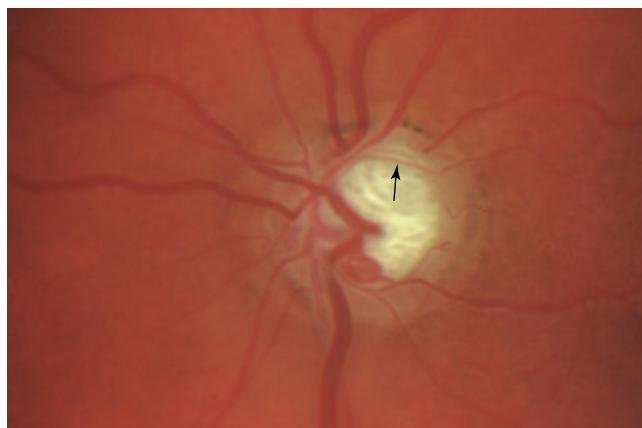


FIGURE 10-10 Baring of the superior circumlinear vessel (arrow).

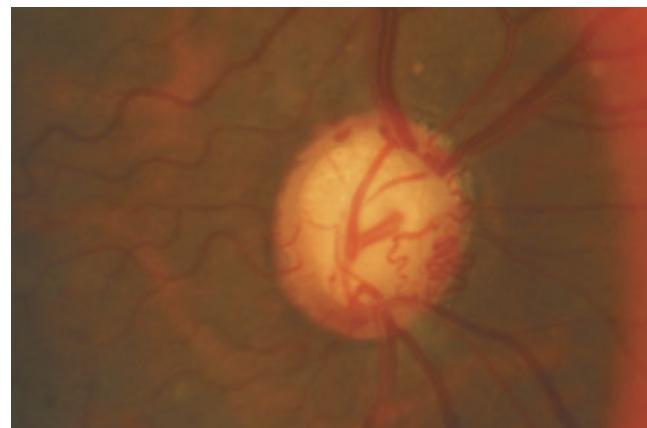


FIGURE 10-11 Collateral disc vessels in a patient with advanced glaucoma.

either with or without neural rim loss. However, rim pallor is unusual in chronic glaucoma. Although compressive optic neuropathy, ischemic optic neuropathy (especially arteritic), and optic neuritis may all resemble glaucoma, these conditions generally have neural rim pallor that is out of proportion to the degree of cupping. Pallor of the neural rim is a useful sign of nonglaucomatous atrophy, with 94% specificity.¹¹⁶

PEARL... Pallor of the neural rim is a useful sign of nonglaucomatous atrophy.

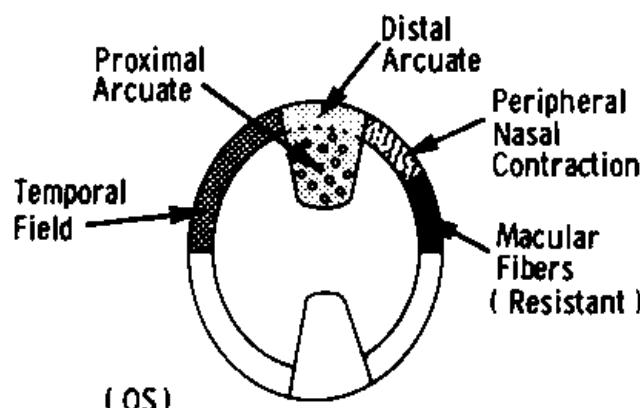


FIGURE 10-12 Map of the optic disc, illustrating the various areas of disc damage and the corresponding visual field defects. (Reprinted from Read RM, Spaeth GL. The practical clinical appraisal of the optic disc in glaucoma: the natural history of cup progression and some specific disc-field correlation. *Trans Am Ophthalmol Otolaryngol* 1974;78:225–274, with permission of the authors and publishers.)

CORRELATION BETWEEN STRUCTURE AND FUNCTION

An experienced examiner should be able to predict a visual field defect based on the appearance of the glaucomatous optic nerve damage (Fig. 10-12). For example, an optic nerve head with focal loss of the inferior neural rim should have a corresponding superior arcuate visual field defect. A diffuse narrowing of the neural rim may show a diffuse decrease in sensitivity of the visual field.

SPECIAL CONSIDERATION

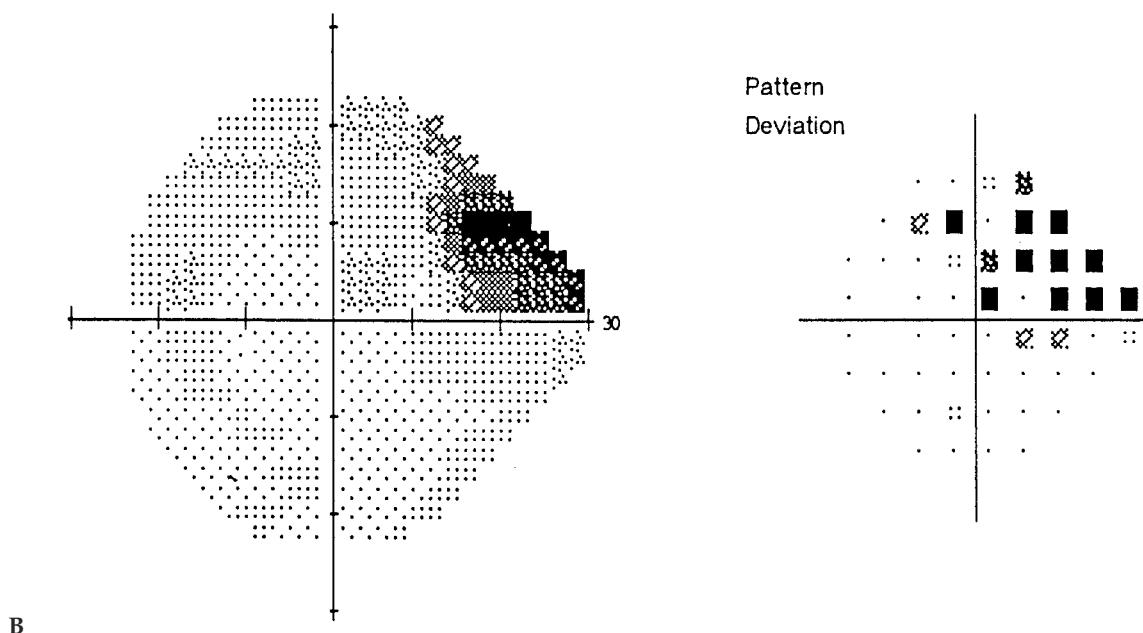
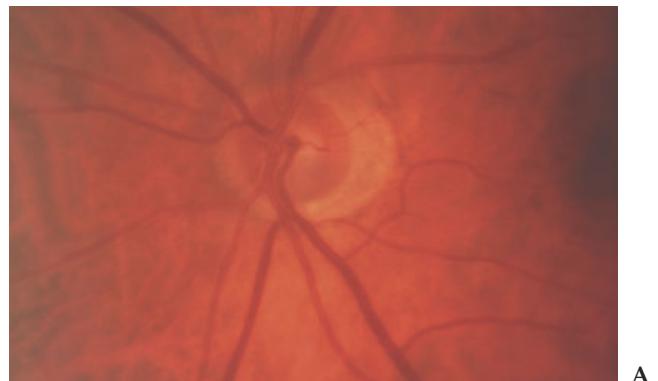
Lack of appropriate anatomic correlation between the location and extent of disc rim loss and the visual field appearance should alert the clinician to diagnostic possibilities other than glaucoma.

Nonglaucomatous changes, such as optic nerve head drusen and retinal scars, may mimic the appearance of glaucomatous visual field defects. Glaucomatous eyes with small discs tend to have misleadingly small cups. Glaucomatous eyes with low cup-to-disc ratios have a significantly smaller disc area than normal subjects and glaucoma patients with high cup-to-disc ratios (Fig. 10-13A,B).¹¹⁷

PITFALL... Glaucomatous eyes with small discs may have misleadingly low cup-to-disc ratios.

Correlating optic nerve appearance with the visual field also includes understanding the temporal pattern of damage. In general, optic nerve head changes tend to

FIGURE 10-13 (A) Small left optic disc of a primary open-angle glaucoma patient. Note the narrow inferior neural rim, the peripapillary halo, and the misleadingly low cup-to-disc ratio. (B) Visual field documents a superior nasal step and a paracentral scotoma.



precede measurable visual field abnormalities in early glaucoma.^{7-9,13,14} In advanced glaucoma, however, visual field defects usually progress without noticeable changes to an already extensively cupped optic nerve.

PHENOTYPES OF GLAUCOMATOUS OPTIC NERVE DAMAGE

Four clinical patterns of glaucomatous optic nerve appearance have been described: focal ischemic, senile-sclerotic, hyperbaric, and myopic. The focal ischemic pattern describes a subgroup of patients with low-tension glaucoma and dense, isolated, paracentral scotomas associated with focal thinning of the neural rim, typically inferotemporally.¹¹⁸ Levene has observed a greater degree of cupping than would be predicted from the amount of visual field loss in patients with low-tension glaucoma compared with glaucoma of high-tension type.¹¹⁹

The senile-sclerotic pattern is characterized by saucerization of the cup and a pale, "moth-eaten" disc

rim. In one study, this pattern was associated with extensive choroidal sclerosis and peripapillary choroidal atrophy.¹²⁰ In the same study, young patients with high IOP had generalized, cylindrical cupping without sloping of the disc rim. This is often referred to as the hyperbaric pattern. Myopic patients with glaucoma often have tilted optic nerve heads with temporal rim sloping and scleral crescents. The senile-sclerotic and myopic patterns can be the most difficult to identify as glaucomatous in the absence of other information, such as risk factors and visual field and nerve fiber layer defects.

A glaucoma patient does not have to fit into any of these groups. Some patients have characteristics that represent a combination of these types, and other patterns or other phenotypes may yet be described. The identification of phenotypic subtypes of nerve damage in primary open-angle glaucoma may eventually make the course of the disease more readily predictable and may also be associated with genotypes that are yet to be discovered.

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QUANTITATIVE IMAGING OF THE OPTIC DISC

Balwantray C. Chauhan, Ph.D.

The diagnosis and management of glaucoma depend heavily on assessing the appearance of the optic disc. Clinicians have traditionally used subjective parameters, such as the cup-to-disc ratio¹ along with estimates of the disc size, to determine the presence of glaucoma and to detect progression of glaucomatous damage. Although initial attempts at quantifying structural parameters used conventional photography, new imaging techniques, including digital fundus cameras, video-based acquisition systems, confocal scanning laser ophthalmoscopes, optical coherence tomography, and new applications for ultrasound, provide new opportunities for objective data acquisition. Currently, instruments combining confocal scanning laser ophthalmoscopy with sophisticated, computer-assisted analysis have enjoyed the greatest success in characterizing optic disc topography and detecting subtle changes over time. Although the techniques described in this chapter cannot replace clinical judgment, their great promise for supplying and analyzing quantitative, objective data suggests that their role in glaucoma care will continue to expand.

QUANTITATIVE MANUAL ANALYSIS OF PHOTOGRAPHIC IMAGES

Quantitative analysis of the optic disc contour using fundus photography began several decades ago. In its simplest form, the observer estimates linear measurements, such as cup-to-disc ratio, minimum rim-to-disc ratio, and location of the minimum rim, either by viewing mono- or stereoscopic prints of the optic disc or by projecting slides of the disc on a screen. Quantitative measurements of the optic disc, cup, and neuroretinal rim area utilize planimetry, in which the observer manually traces the optic disc and cup borders as seen with stereoscopic disc photographs and computes the enclosed areas.² To determine

actual sizes in absolute units, planimetric values are usually corrected for the magnification effects of the eye by accounting for its refraction, axial length, and corneal curvature.³ Depth measurements of the optic cup can be made using a technique called photogrammetry,^{4,5} where an operator measures relative depth from stereo photographs using a stereoplotter. Because the stereoscopic base, or the angular separation between the stereo pairs, is critical, this technique works optimally when images are obtained by simultaneous stereo photography.

In addition to information about the contour of the optic disc, some authors have used densitometry to quantify its pallor by measuring the spectrum of light reflected from the optic disc.⁶ Increased optic disc pallor usually accompanies morphological changes in the glaucomatous optic cup, and results from loss of vascularity and/or thinning of neural tissue, both of which allow greater light reflection from the lamina cribrosa.

QUANTITATIVE AUTOMATED ANALYSIS OF PHOTOGRAPHIC OR VIDEOGRAPHIC IMAGES

In the last 20 years, automated devices capable of obtaining depth or height information using photogrammatic analysis of stereo images of the optic disc have been introduced. The Optic Nerve Head Analyzer (Rodenstock Instruments GmbH, Munich, Germany) projects a set of stripes onto the optic disc and captures simultaneous stereo images using a pair of video cameras with known angular separation (stereo base). Calculating the deformation of the stripes across the various contours of the disc and correlating information from the two images provides information about topographic depth and volumetric optic disc parameters, in addition to the planar measurements such as disc and cup area.⁷

Several studies, conducted in the 1980s, showed that the reproducibility of planar measurements [coefficient of variation, defined as $(\text{standard deviation}/\text{mean}) \times 100\%$] with this technique was under 10%, whereas that of volumetric measurements was under 20%.⁸ Two other devices, the Topcon Imagenet (Topcon Instruments Corporation, Paramus, NJ) and the Humphrey Retinal Analyzer (Humphrey Instruments, Dublin, Calif) also use stereo images captured either through a video camera or via digitized slides to provide image enhancement and topographic information of the optic disc. Experience with these two devices is relatively limited and only the Topcon Imagenet system is currently available.

The Glaucoma-Scope (Ophthalmic Imaging Systems, Sacramento, Calif) also measures topography with a method similar to studying the deformation of stripes projected on the optic disc. Unlike the devices already described, the Glaucoma-Scope uses a monoscopic video system to capture the image of the optic disc. Although it measures depth in approximately 9,000 points in the imaged area, this instrument uses interpolation to calculate topography values at considerably more locations, in addition to optic disc parameters such as cup-to-disc area.

Although the Glaucoma-Scope has been used in clinical⁹ and experimental studies,¹⁰ it is no longer manufactured.

CONFOCAL SCANNING LASER TOMOGRAPHY

Confocal scanning laser tomography is currently the most widespread nonphotographic technique for imaging the optic disc and peripapillary retina in glaucoma. This technique has evolved from confocal scanning laser ophthalmoscopy, which was introduced in the 1980s¹¹ and was used primarily for two-dimensional imaging of the retina, angiography, and microperimetry. Although its forerunner, the Laser Tomographic Scanner¹² (Heidelberg Instruments GmbH, Heidelberg, Germany), is no longer available, the considerable scientific work undertaken with this earlier tomographic device has resulted in improvements in hardware and software that make today's commercial devices better and more affordable.

Currently, two available instruments use scanning laser tomography, the Heidelberg Retina Tomograph (Heidelberg Engineering GmbH, Dossenheim, Germany) and the TopSS (Laser Diagnostics Technologies, San Diego, Calif). Although both devices use similar principles and essentially generate the same type of data, they possess some differences in both hardware and software. Almost all the published clinical and experimental work to date is based on the Heidelberg Retina Tomograph.

INSTRUMENTATION

These instruments consist of a camera head mounted on a slit-lamp-type stand, a control panel for operation, and a computer for control and for the display, acquisition, processing, and storage of data. The camera head contains a diode laser (wavelength 670 nm in the Heidelberg Retina Tomograph and 780 nm in the TopSS) and a confocal optical system. This system (Fig. 11-1) contains a pinhole situated in front of the detector, and a photodiode that detects the intensity of the light reflected from the fundus. The pinhole ensures that the detector captures light reflected from the focal plane of the laser and largely eliminates light reflected from deeper or shallower locations. The spot size on the fundus is approximately 10 μm . By scanning both horizontally and vertically in one focal plane, the instrument acquires a two-dimensional confocal image. Varying the depth of the focal plane allows acquisition of images from other planes along the z-axis (perpendicular to the optical axis).

The image resolution at each plane is 256 X 256 picture elements (pixels), resulting in 65,536 measurements per image. An entire scan contains 32 confocal section images that are equally spaced along the z-axis, whereas

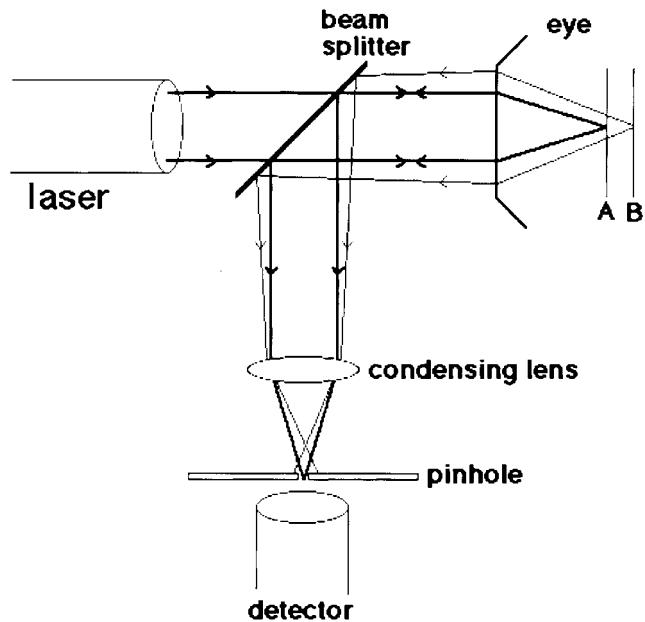


FIGURE 11-1 Simplified schema of a confocal system. The laser beam comes to a sharp focus on the retina (A) assuming an emmetropic eye and zero vergence of the laser beam. Light reflected from A (bold ray path) leaves the eye and is deflected by the beam splitter. A condensing lens brings these rays to a focus at the confocal pinhole (placed at the focal plane of the condensing lens). The detector detects light from A maximally. Light coming from B (lighter ray path) is largely eliminated from detection because of the pinhole. (From Chauhan BC. Interpreting technology: confocal scanning laser tomography. *Can J Ophthalmol* 1996;31:152. Reproduced with permission from Canadian Journal of Ophthalmology.)

the operator can vary the total scan depth and scan area, depending on the size of the optic disc and depth of the optic cup. The total image acquisition times for the Heidelberg retina tomograph and the TopSS are 1.6 seconds and 0.9 seconds, respectively. The Heidelberg Retina Tomograph II was introduced in 1999. This is a compact device with an image resolution of 384×384 pixels over a scan angle of 15 degrees. A total of 16 equally-spaced confocal section images per 1 mm of scan depth are acquired. New features include automatic setting of scan depth, fine focus, and multiple sets of confocal section images to compute the mean topography.

Image Processing

Because of the relatively long acquisition time and the high resolution of these devices, the confocal section images must be aligned to correct for any horizontal or vertical eye movements during image acquisition. This alignment procedure ensures that each pixel location in all of the section images corresponds to the same transverse location on the fundus, allowing a graphical representation of the intensity values for that location (the intensity, or z-profile) over all image depths (Fig. 11–2). This intensity profile determines both the reflectivity (given by the area under the intensity profile) and depth (defined as the location of maximum intensity along the z-axis) of the imaged location. Using the intensity and depth values of each pixel, the software generates a topography and reflectivity image (Fig. 11–3A, B).

PEARL... When imaging eyes with astigmatism greater than 1 diopter, it is better to acquire images with spectacles if the patient has nontinted, single-vision lenses.

An imaging session consists of multiple (usually three to five) scans, which are then aligned to obtain a mean

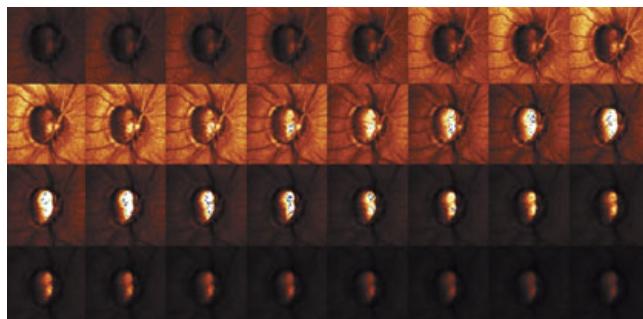


FIGURE 11-2 Color-coded confocal section images through a glaucomatous optic disc. The top left image shows the first image with the laser focused in front of the retina, whereas the bottom right shows the last image with the laser focused at the level of the retrolaminar optic nerve.

reflectivity and topography image for that session. This alignment procedure, which also accounts for lateral, rotational, and depth differences between the individual images, can also be used to compare the mean images from different session dates and to help determine if progression has occurred over time.

Computation of Optic Disc Parameters

After determining a topography image (either a single scan or a mean of several scans), the operating software can calculate various optic disc parameters. Using a computer mouse, the operator manually draws the border of the optic disc (a contour line), which is stored in memory and then exported to subsequent images of the same eye, thus ensuring a consistent disc border for the various parameter calculations. A reference plane, based on the height of the contour line, is determined and used to delineate the “top” of the optic cup. Although controversial, the default position of the reference plane in the current release of the Heidelberg Retina Tomograph (v. 2.01) lies 50 μm below the mean height of the contour line between 4 and 10 degrees inferior to the horizontal midline. This represents the part of the papillomacular bundle probably affected last in glaucoma and therefore the most stable position for a reference plane.

SPECIAL CONSIDERATION

Although the reference plane setting in scanning tomography is arbitrary, it must be kept identical for patient follow-up.

The parameters themselves appear in absolute units, calculated from a simplified model that uses the refraction of the eye (automatically measured when the camera is focused for image acquisition) and a standard corneal curvature.



FIGURE 11-3 (A) Color-coded topography and (B) reflectivity images obtained after processing of the 32 confocal section images is shown. In the topography image, the darkest locations are the most superficial whereas the brightest locations are the deepest.

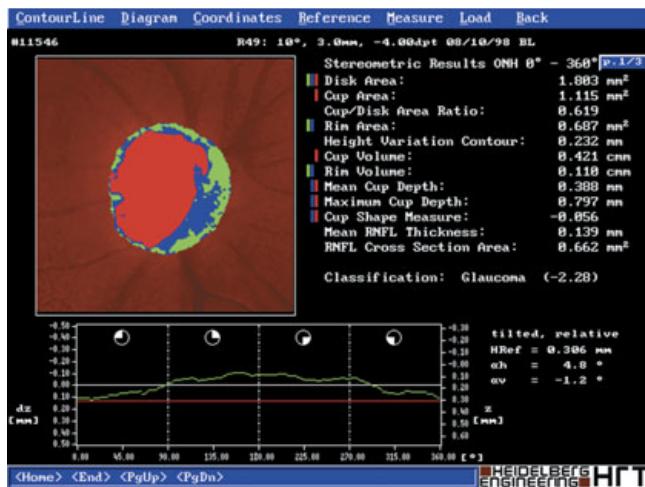


FIGURE 11-4 Stereometric analysis from the Heidelberg Retina Tomograph after the disc border of the eye shown in Figures 11-3 and 11-5 has been defined. Red area within the disc delineates the optic cup. Green line (below) shows the circumferential height of the contour line. Some of the parameters include optic disc and neuroretinal rim area, cup and rim volumes, and cup shape measure.

The patient's axial length and corneal curvature can be entered into the database for more precise measurements but do not have to be repeated for patient follow-up because these biometric data usually do not change. Calculated parameters include the optic disc area, cup-to-disc ratio, neuroretinal rim area, cup volume, and neuroretinal rim volume, as well as a measure of the shape of the cup (Fig. 11-4).

CLINICAL UTILITY

The primary utility of any optic disc imaging technique is to determine (1) whether there is abnormality (detection) and (2) whether there is a change (progression) in the optic disc.

Detecting a glaucomatous optic disc using optic disc parameters depends on how much the distribution of each parameter in glaucoma patients overlaps with that of the normal population. Several studies have demonstrated a large variation in the size of normal optic discs.¹³ Given that the cup-to-disc ratio and neuroretinal rim area are closely related to disc size,¹⁴ these parameters in normal patients will also vary widely and, therefore, overlap extensively with the glaucoma population. In fact, the Baltimore Eye Survey has shown that cup-to-disc ratio and minimum rim width in isolation discriminate poorly between normal and glaucomatous eyes.¹⁵

There are many clinical features of the optic disc used to make a diagnosis that cannot be captured in numerical indices, such as color change and alterations in blood vessel pattern. Many studies, however, have used a variety of approaches to separate normal from glaucomatous optic discs, as discussed in the following section *Sensitivity and Specificity*.

Detecting progression depends on the ability to observe a change in topography over time. Many statistical approaches have been developed for this purpose, all defining a significant change as that which exceeds the physiological variability of the measurements themselves.

PEARL... Optimum patient follow-up with scanning laser tomography requires that the optic disc be centered in the image frame.

The most clinically intuitive approach is to determine how optic disc parameters, such as the neuroretinal rim area or the cup volume, behave over time. This requires importing the contour line defined at baseline to subsequent images, thus ensuring that the area defined as the optic disc remains constant from one exam to the next. Progression is then determined either by comparing parameters from follow-up examinations to their baseline, or by examining the evidence for a trend. In addition to a constant contour line, both approaches require that the reference plane be kept at a constant depth, if not using the default value. Another approach characterizes regional variability within individuals and determines the probability of detecting localized change, without relying on the traditional parameters and the reference plane.^{16,17}

CLINICAL STUDIES

Variability

The utility of any optic disc-imaging device depends on the reproducibility or variability of repeated measurements in the same eye. Theoretically, measurements with low variability can detect small amounts of change, which might otherwise be missed by measurements with a higher variability. Several investigators have studied the variability of optic disc parameters^{18–22} as well as individual topography measurements^{20,21,23–26} with the Heidelberg Retina Tomograph. Generally, the variability of parameters ranges from around 5 to 10% (coefficient of variation), with measurements of disc and neuroretinal rim area varying less than parameters such as height variation of the contour line and cup shape measure.

One study showed that variability measurements in a model eye were several orders of magnitude lower than in human subjects²⁷ suggesting that physiological variations such as ocular pulse and alignment errors are a major cause of measurement variability. Measurement of single pixel heights in glaucoma patients and normals is around 30 and 25 µm (standard deviation), respectively, though almost all the published studies used older software versions (v. 1.11 or earlier). The current version (v. 2.01) contains revised image alignment algorithms, which decrease average variability by 25 to 30% and reduce variability in

areas with steep contours by a factor of 2 or more. The standard deviation of single-pixel height measurements in normal subjects with the TopSS system has been reported at around 40 µm.²⁸

Variability increases with age,²⁵ steep topographic contours (cup borders),^{25,29} media opacities,^{30,31} and decreasing pupil size,^{21,32} although image quality probably only deteriorates significantly in pupils <3 mm, particularly in the presence of media opacities.³¹ The cardiac cycle also affects variability.³³ One study showed that the short- and long-term variability components of variability in normal subjects does not appear to be different, suggesting that practical estimates of variability can be obtained in a single session.³⁴ Operator skill can also influence variability because this controls many factors affecting image quality, such as patient alignment, proper scan depth, and judgment in regard to media opacity and pupil size.

Validity

Studies assessing the accuracy of parameters measured by the Heidelberg Retina Tomograph are generally conflicting, showing measurements of the neuroretinal rim to be larger,^{35,36} smaller,^{37,38} or almost identical³⁹ to results from manual methods using stereo photographs. One study, comparing measurements with the Heidelberg Retina Tomograph to direct optic disc measurements during vitrectomy, showed a measurement error of around 3%.⁴⁰

CONTROVERSY

The agreement between scanning laser tomography and conventional techniques in measuring optic disc indices has yielded mixed results, with studies showing larger, smaller, or identical estimates. These differences may be important for diagnostic purposes but not for follow-up studies.

Sensitivity and Specificity

Determining the sensitivity and specificity of these instruments in detecting glaucomatous optic nerve damage can illustrate the potential of this rapid imaging technique to supplement time-consuming perimetry. Numerous studies have shown that optic disc parameters from confocal scanning laser tomography, particularly the cup shape measure, correlate well with visual field damage.⁴¹⁻⁴⁵ Studies of the Heidelberg Retina Tomograph in a clinical setting generally report 80 to 90% sensitivity and specificity for a single or combination of parameters using multivariate approaches.^{26,41,46-49} Because of the inevitable selection bias in a clinical study, these figures may be lower in unselected samples.

Detecting Progression

Although the value of confocal scanning laser tomography as a one-time, definitive test for diagnosing glaucoma is uncertain, recognizing progression of glaucomatous damage represents its most significant potential use. In contrast to conventional stereophotography, scanning laser tomography can detect alterations in optic disc topography following pharmacologically and surgically reduced intraocular pressure.^{50,51}

One new method for detecting progression is based on estimating variability in very small areas of the image and then comparing the change in topographic height between a baseline and follow-up image.^{16,17,52} A probability value is then computed for each corresponding small area, indicating the likelihood of the change falling within the expected variability. Using these values for all areas, a probability map is then generated. Evidence with this technique suggests that confocal scanning laser tomography can readily detect optic disc changes in eyes with only subtle change by conventional optic disc photography and none by visual field analysis (Fig. 11-5A-C).⁵³

THE CURRENT STATUS AND THE FUTURE OF CONFOCAL SCANNING LASER TOMOGRAPHY

Although automated static perimetry is currently the accepted technique for making the definitive diagnosis of glaucoma, it relies heavily on the patient's subjective participation, and fluctuation from test to test is fairly high. Because optic nerve changes may precede visual field loss, detecting early glaucomatous optic disc damage is sometimes the only way to differentiate between true progressive field changes and random fluctuation. However, clinical assessment alone cannot accurately document disc topography. Although serial photographs can show progressive change in discs long before the development of visual field loss,⁵⁴ quantification is difficult and traditional photographic techniques suffer from many drawbacks, including sensitivity to pupil size and media opacities.

Most of the earlier quantitative optic disc-imaging devices are now unavailable, but confocal scanning laser tomography is becoming widely used in ophthalmic practice. It is rapid and easy to administer. Because there is no flash, it is more comfortable for the patient than conventional photography, and the images can be processed online for rapid stereometric analysis. Good-quality images are generally possible without pupil dilation, although this may still be necessary in patients on miotics, particularly in the presence of a cataract.

Confocal scanning laser tomography offers several options for analyzing optic disc and peripapillary topography, ranging from the calculation of standard optic disc parameters to interactive horizontal and vertical cross sections of the imaged areas. Hardware upgrades cur-

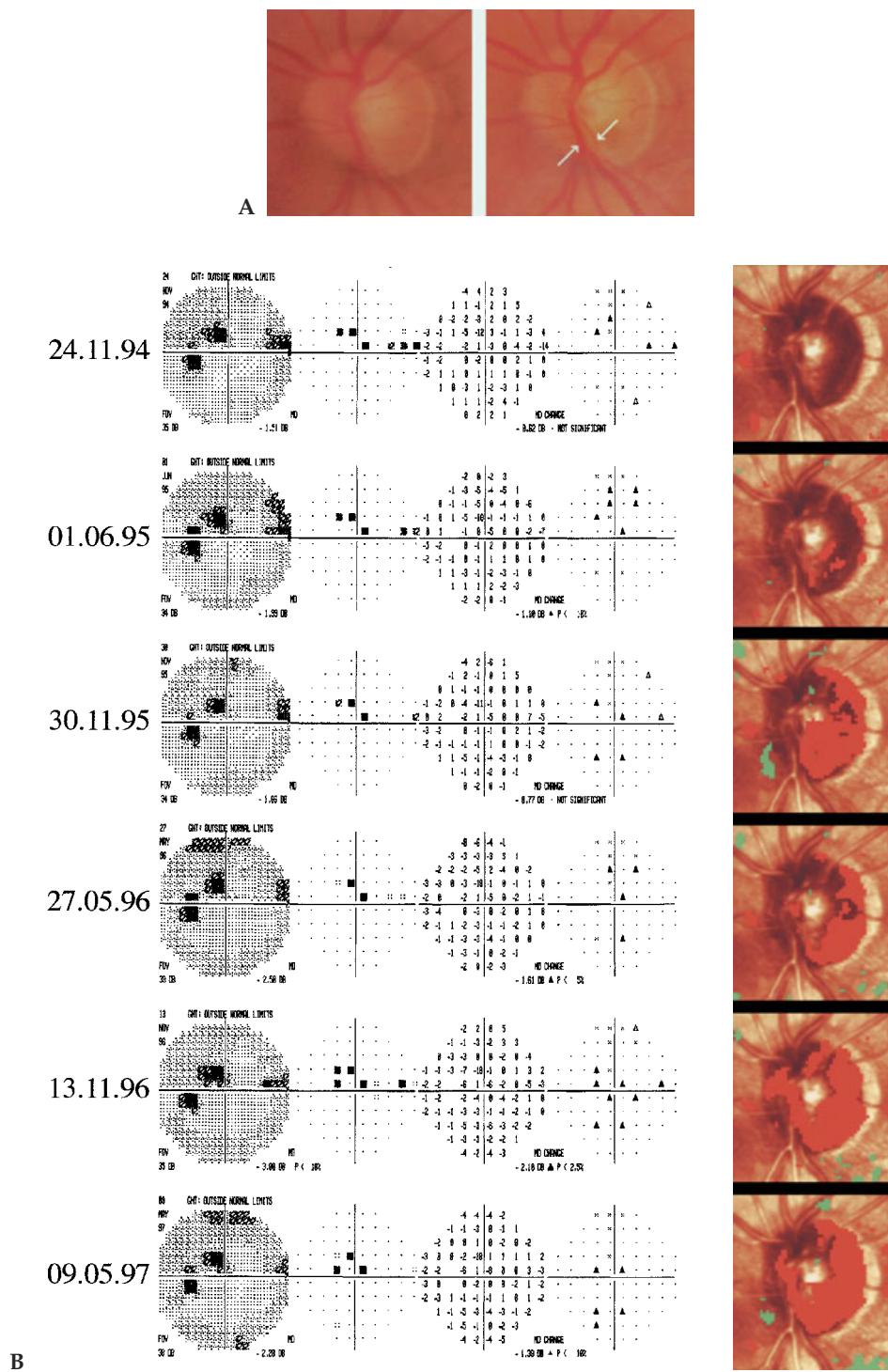


FIGURE 11-5 Part of the 6-monthly follow-up of the left eye of a glaucoma patient. (A) Optic disc photographs taken on 11.24.94 (left) and 09.05.97 (right) showing subtle change in vessel configuration (arrows). (B) STATPAC Glaucoma Change Probability showed no visual field progression. (C) Probability maps from a new technique using data from confocal scanning laser tomography recorded on the same days as the visual field show substantial progressive collapse of disc rim tissue (red areas), particularly in the inferior temporal quadrant.

rently include confocal scanning laser Doppler flowmetry with the Heidelberg Retina Tomograph, and indocyanine green angiography for the TopSS system.

Confocal scanning laser tomography does possess some disadvantages. There is currently no consensus on what changes are clinically meaningful in either the optic disc parameters or the techniques that use probability maps, although this information may develop in time. Also, peculiar reflectance properties in the fovea and

peripapillary temporal crescents can provide erroneous topographical measurements and confound meaningful interpretation. Finally, the cost of the instrumentation may limit its use to clinics caring for large numbers of glaucoma patients and glaucoma suspects.

Confocal scanning laser tomography should be carried out in individuals at a higher risk for developing glaucoma such as those with ocular hypertension and those with suspicious discs. In these cases, a change in the disc

without a change in the visual field may provide valuable clinical information. In patients with established glaucoma, images should be acquired at least as frequently as visual fields.

Although there is little doubt that confocal scanning laser tomography offers many advantages over conventional techniques of assessing the optic disc, further clinical and scientific study is necessary to confirm its place in the glaucoma practice. In the meantime, good-quality stereo photographs combined with prudent clinical judgment are still important for documenting and monitoring the optic disc in the management of glaucoma.

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EVALUATING THE NERVE FIBER LAYER

Pait Teesalu M.D., Ph.D., and P. Juhani Airaksinen, M.D., Ph.D.

Glaucomatous optic nerve damage produces thinning and decreased visibility of the retinal nerve fiber layer (RNFL). Clinically, the RNFL can be assessed by either ophthalmoscopy or wide-angle, red-free photographs. By helping the examiner identify nerve fiber loss, these methods provide an important adjunct for assessing the condition of the optic nerve head and the validity of visual field findings. However, these techniques supply only qualitative information and have a limited capacity for assessing long-term behavior of the nerve fiber layer.

Recently, three high-technology methods have evolved to provide an objective measurement of the nerve fiber layer. The Nerve Fiber Analyzer (NFA) (Laser Diagnostic Technologies, San Diego, California) provides an estimate of the peripapillary RNFL thickness using the polarization properties of the axon bundles, whereas optical coherence tomography (OCT) assesses RNFL thickness by measuring its light reflection properties. The third of these instruments, the Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering GmbH, Heidelberg, Germany), indirectly measures the thickness of the RNFL at the optic disc margin.

Despite the detailed measurements provided by these methods and instruments, wide variations in the normal RNFL and the subtle nature of early glaucomatous changes may limit their usefulness in differentiating between normal and glaucomatous eyes. The greatest potential of these techniques may lie in their ability to detect changes in the RNFL over time.

ANATOMY

The RNFL represents the innermost layer of the fundus and is separated from the vitreous by the internal limiting membrane. The RNFL contains retinal ganglion cell axons imbedded in astrocytes and the processes of Müller cells

(Fig. 12-1A–C). Through these fibers, the retinal ganglion cells conduct visual information from the photoreceptors to the next synapse, in the lateral geniculate body.

Clinically, a healthy RNFL appears slightly opaque, with radially oriented striations covering the small vessels (Fig. 12-2A,B). These striations (the axon bundles) are visible because light is reflected from the nerve fiber bundles and the intervening glial septa. The upper and lower temporal fibers form an arch around the macula and are called the arcuate nerve fiber bundles. This is the very pattern that determines the typical appearance of glaucomatous arcuate visual field defects. The superior and inferior temporal bundles are separated by the temporal raphe that extends horizontally into the temporal retinal periphery from the foveola. In contrast, the papillomacular bundles have almost a straight horizontal course, whereas the nasal nerve fiber bundles proceed radially into the optic disc.

Fibers that arise from the more peripheral fundus generally lie deeper in the RNFL, closer to the pigment epithelium (Fig. 12-3). Those originating from more proximal ganglion cells pierce these deep fiber bundles and proceed to the optic disc in the superficial nerve fiber layer, closer to the vitreous. All RNFL axons coalesce at the optic disc, turn posteriorly, and form the neuroretinal rim of the optic nerve head. Superficial nerve fiber bundles, originating nearer to the optic disc, generally reside in the central regions of the optic nerve head, whereas those arising from the peripheral fundus tend to lie closer to the edge of the chorioscleral canal.^{1,2}

Overall, the nerve fiber layer increases in thickness as it approaches the optic disc. It is thickest, and most visible, in the upper and lower temporal arcuate regions (the vertical poles of the optic disc), where it measures up to 300 µm deep.³ By contrast, the nerve fiber layer is much less visible in the nasal and papillomacular areas, where it is only one fifth as thick.

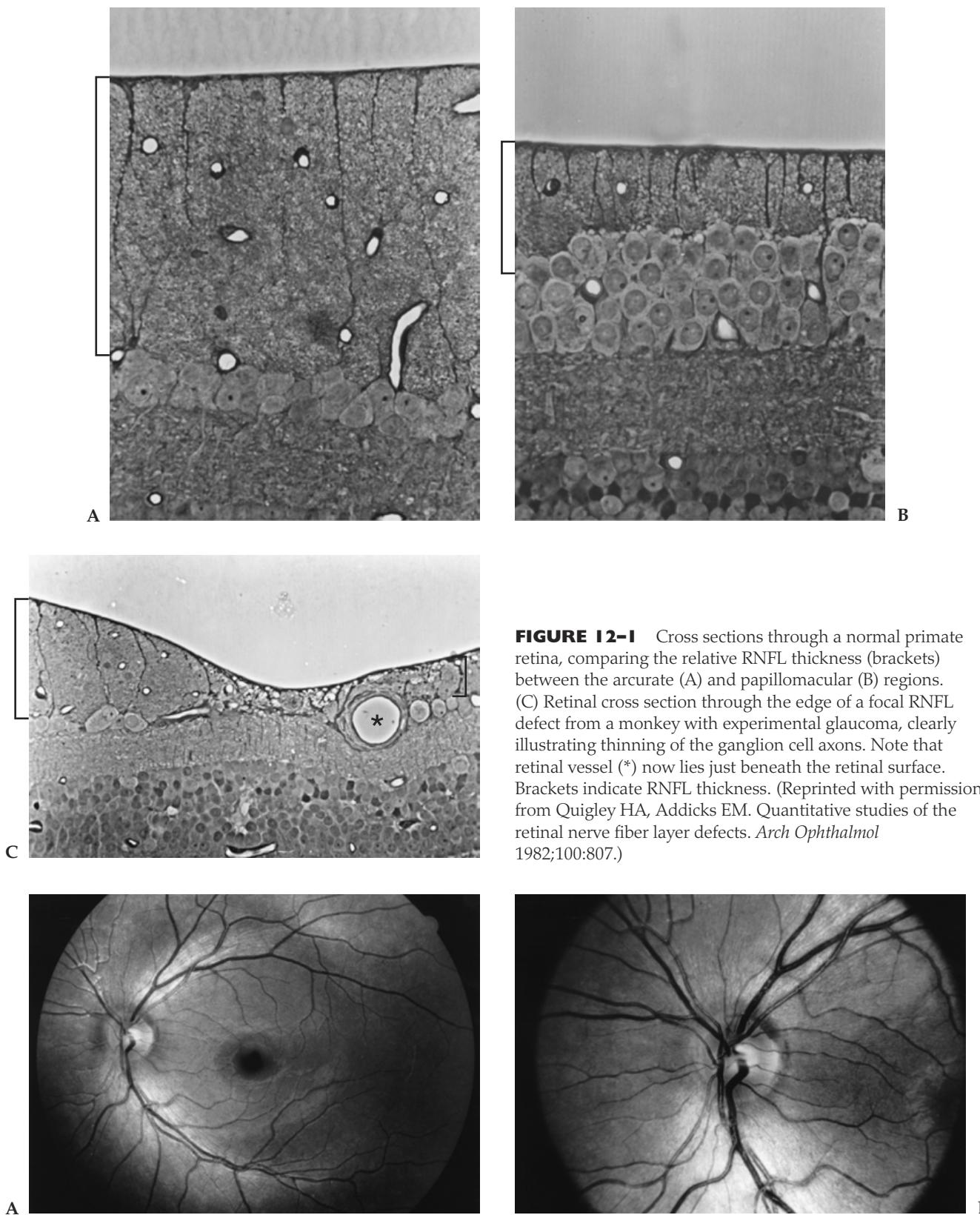


FIGURE 12-1 Cross sections through a normal primate retina, comparing the relative RNFL thickness (brackets) between the arcurate (A) and papillomacular (B) regions. (C) Retinal cross section through the edge of a focal RNFL defect from a monkey with experimental glaucoma, clearly illustrating thinning of the ganglion cell axons. Note that retinal vessel (*) now lies just beneath the retinal surface. Brackets indicate RNFL thickness. (Reprinted with permission from Quigley HA, Addicks EM. Quantitative studies of the retinal nerve fiber layer defects. *Arch Ophthalmol* 1982;100:807.)

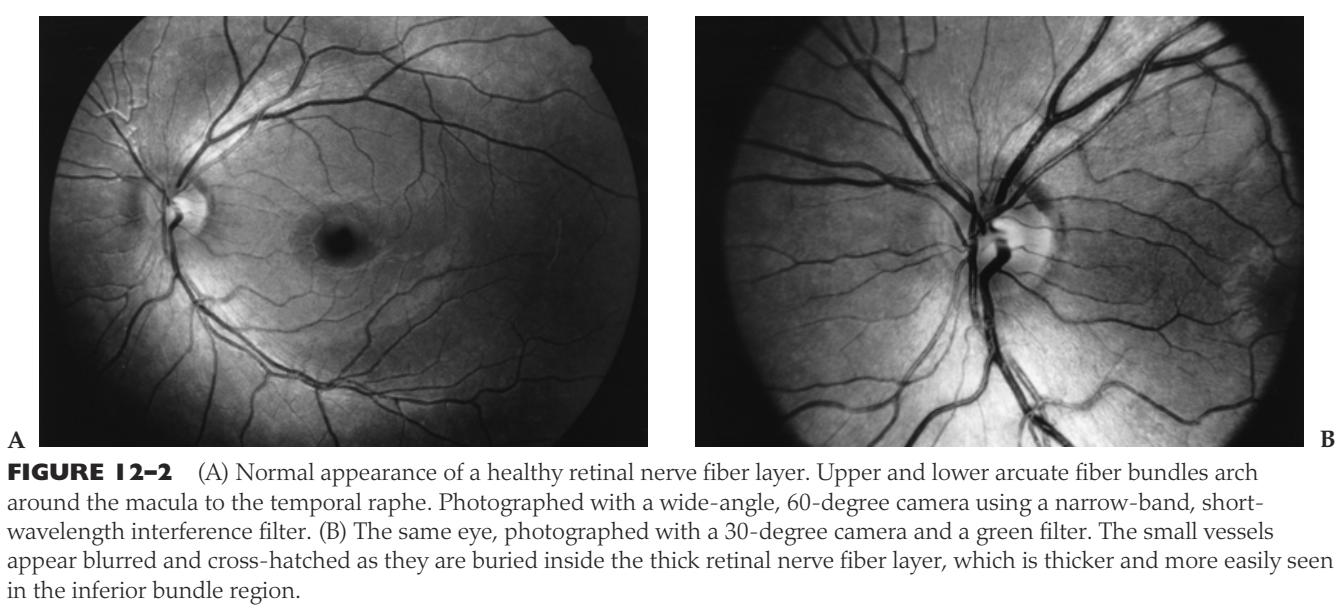


FIGURE 12-2 (A) Normal appearance of a healthy retinal nerve fiber layer. Upper and lower arcuate fiber bundles arch around the macula to the temporal raphe. Photographed with a wide-angle, 60-degree camera using a narrow-band, short-wavelength interference filter. (B) The same eye, photographed with a 30-degree camera and a green filter. The small vessels appear blurred and cross-hatched as they are buried inside the thick retinal nerve fiber layer, which is thicker and more easily seen in the inferior bundle region.

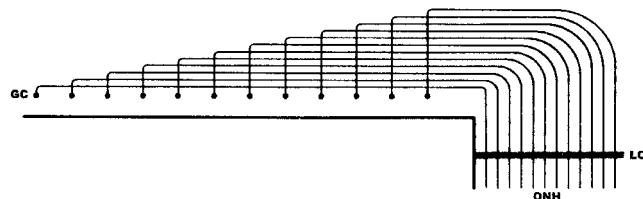


FIGURE 12-3 Schematic illustration of the topographic organization of the nerve fibers in the retina and the optic disc. Axons that originate from the peripheral fundus tend to lie in the outer regions of the optic nerve.

EXAMINATION TECHNIQUES

RETINAL NERVE FIBER LAYER FUNDUSCOPY

In 1913, Alfred Vogt described the visibility of the nerve fiber bundles by ophthalmoscopy.⁴ The loss of nerve fibers decreases this visibility. In white light, RNFL atrophy makes the fundus appear darker red, with reduced visibility of the normal striation pattern. Green or red-free light provides much better visibility of the nerve fiber layer and its defects. This short wavelength light does not penetrate the RNFL but is instead reflected from the superficial layers of the retina back to the observer. In areas where the nerve fiber layer is destroyed, the underlying pigment epithelium absorbs the light and makes the defective areas appear darker, with less retinal surface detail than in the healthy areas.

PEARL... Direct ophthalmoscopy using green light can provide good visibility of the nerve fiber layer and its defects up to one to two disc diameters away from the optic disc.

An ophthalmoscope can reveal the striped pattern of the RNFL approximately one to two disc diameters away from the optic disc. With the slit-lamp and the Volk lens or a contact lens, the nerve fiber bundles can be seen up to the level of macula. Adjusting the slit beam broad and flat, almost quadratic, allows the examiner to view larger areas at a time. However, a small slit beam, or small spot size with direct ophthalmoscope, may minimize reflections from the tear film and the lens and can improve the visibility of the RNFL detail. Both techniques have advantages and disadvantages (Table 12-1). Using the visibility of retinal blood vessels to assess the RNFL thickness is an important clinical tool, and is discussed below under qualitative evaluation of the RNFL.

It is always useful first to assess the optic nerve and then see if the appearance of the RNFL confirms the optic disc findings. On the other hand, a localized, wedge-shaped defect in the RNFL can call attention to a specific location on the optic disc, thus helping to detect early disc changes.

Clinical evaluation of the RNFL is difficult to learn, and in many patients, media opacities and pigmentation differences will hamper its routine use for following patient progression or stability. Nevertheless, clinical assessment of the RNFL can help detect subtle or early

TABLE 12-1 CLINICAL TECHNIQUES FOR EXAMINING THE RETINAL NERVE FIBER LAYER

Method	Comments
Direct ophthalmoscopy	Most convenient Requires little patient cooperation Allows rapid comparison of different RNFL regions within the fundus and between eyes High magnification Tear film irregularities can degrade image
Slit-lamp and 78D or 90D lens	Stereoscopic view Broader field of view Sharp image Inverted image Comparison between eyes cumbersome Requires good patient cooperation
Slit-lamp and contact lens	Stereoscopic view Eliminates tear film:air interface for maximum resolution Upright image Comparison between eyes cumbersome Requires good patient cooperation

optic nerve damage, particularly when the optic disc appearance is equivocal or misleading, as in patients with small optic nerve heads. Learning to assess the nerve fiber layer is well worth the effort, and this procedure should always accompany examination of the optic disc.

RETINAL NERVE FIBER LAYER PHOTOGRAPHY

Monochromatic photography is an easier and more permanent way to view the RNFL and can document any defect visible by clinical examination. Although many localized, sector-shaped RNFL defects (Figs. 12-4; 12-5A,B) can



FIGURE 12-4 Retinal nerve fiber layer photograph demonstrates a very early, subtle loss of nerve fibers in the upper arcuate bundle area (arrows) as compared with the corresponding inferior region.

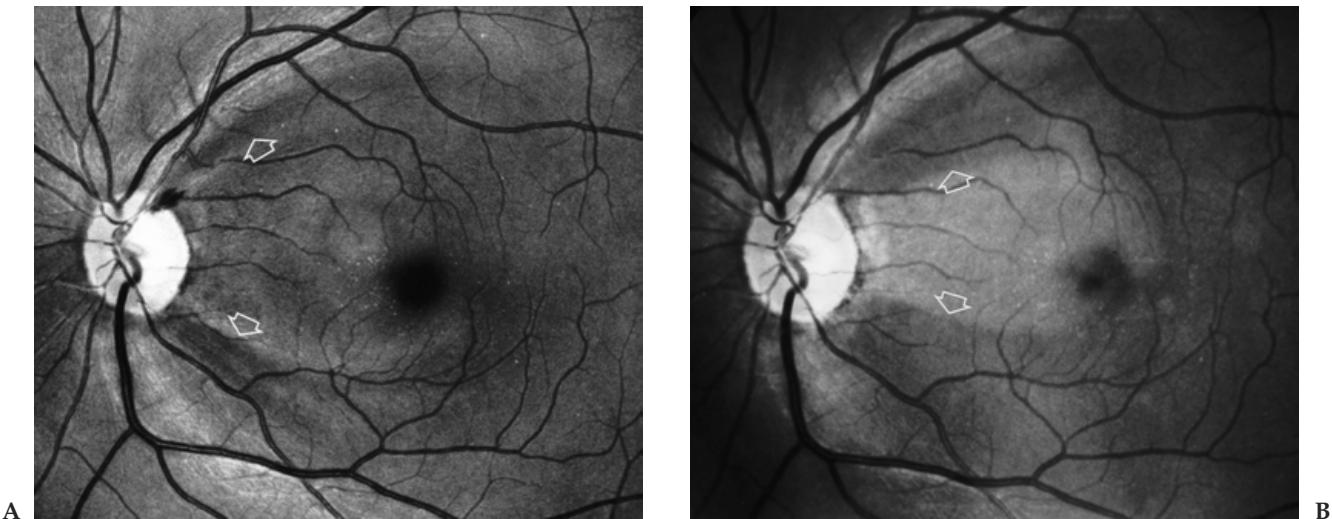


FIGURE 12-5 (A) A distinctly visible arcuate retinal nerve fiber layer (RNFL) defect appears at 1 o'clock (associated with an optic disc splinter hemorrhage) along with a second, wider defect at 4 o'clock position (arrows). (B) The same eye 7 years later. Note widening of the RNFL defects, indicating glaucomatous progression.

be detected easily with funduscopy, some appear only in good-quality photographs. On the other hand, photographs are usually necessary for detecting diffuse or generalized nerve fiber loss.

RNFL photography relies on a blue, narrow-band interference filter with a peak transmittance at 495 nm,^{5,6} and works best with low sensitivity, high-resolution black-and-white film. This is the technique used to produce the RNFL photographs in this chapter. Another method uses color slide images obtained with white light, which are then reproduced on black-and-white film through a green filter.⁷ Although other wavelengths and films have also been used successfully, recently developed digital imaging techniques, discussed in the following text, are gradually supplanting all of these film-based methods.

Because the RNFL itself is difficult to see through the camera, the photographer should focus on blood vessels about half a disc diameter away from the disc. Focusing on the deeper optic disc will put the nerve fibers out of focus.

PITFALL... Measuring intraocular pressure with fluorescein before retinal nerve fiber layer photography can produce a gray, poor-contrast image. This results from the combined effect of the fluorescein exciter filter and absorption of blue light by the yellow, fluorescein-colored tear film.

QUALITATIVE EVALUATION OF THE RETINAL NERVE FIBER LAYER

Several reports affirm that black-and-white photography is a sensitive, useful, and reproducible method for evaluating the RNFL.⁸⁻¹⁰ Intraobserver variation in RNFL assess-

ment is 15%,¹¹ although variation between observers is greater.¹² Slitlike or wedgeshaped local RNFL defects can be easily detected because defective areas appear dark and are outlined sharply against the intact RNFL. The narrowest tip of the wedge is usually found superio- or inferotemporally, either at the optic disc margin or peripapillary area close to the disc (see Fig. 12-5A,B).

PITFALL... Physiological slits or pseudodefects in the retinal nerve fiber layer appear in 10% of normal individuals. In contrast to pathologic defects, they are spindle-shaped, rarely wider than a retinal vessel, and often do not extend to the optic disc.

Diffuse or generalized loss of retinal nerve fibers is considerably more difficult to detect than localized defects. Unfortunately, in half of eyes that develop glaucoma, generalized thinning of the RNFL is the first detectable RNFL abnormality.¹³ This type of loss appears as generalized reduction of the RNFL pattern, and generally gives the retina a mottled appearance (Fig. 12-6). When there is a total or subtotal loss, the fundus appears dark because less or no light is reflected back to the camera.

Evaluating the visibility of blood vessels and capillaries is invaluable in identifying diffuse RNFL damage. In healthy eyes, small vessels look blurred and cross-hatched because they are embedded in the nerve fiber layer. In defective areas, the retinal vessels are covered only by the inner limiting membrane, and the vessel walls stand out sharply (Fig. 12-1). In mild or moderate RNFL atrophy, the first-order branches of vessels are bare, with sharp margins. Complete loss of the RNFL pattern with clearly seen second-order vessels suggests severe, diffuse atrophy.

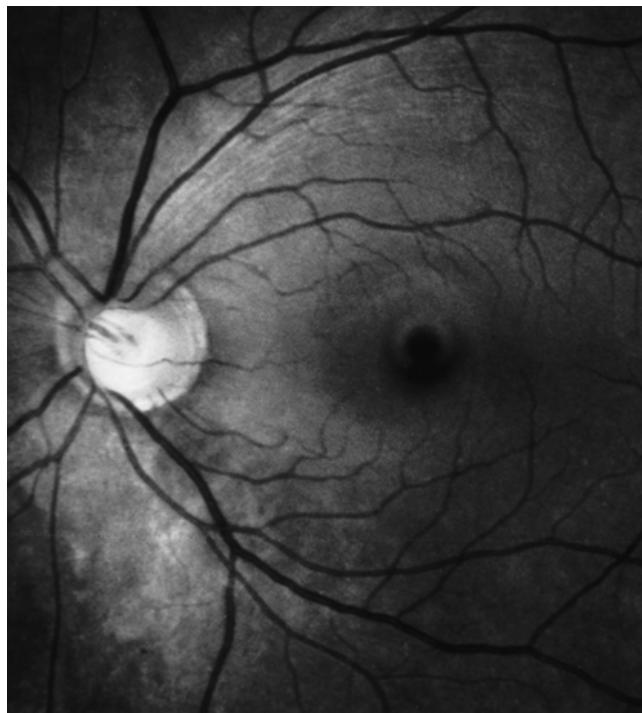


FIGURE 12-6 Diffuse or widespread, generalized thinning of the inferior retinal nerve fiber layer. The small vessels are more visible in the defective area than in the healthier superior area, and as compared with the normal eye shown in Figure 12-2.

It is also useful to compare the visibility of superior and inferior fibers within the same eye. In fact, this comparison of superior to inferior RNFL is the best way to differentiate media haze from mild RNFL atrophy (see Fig. 12-6) because a cataract rarely makes it difficult to see only one half of the RNFL. Because the nerve fiber layer is often more prominent inferiorly, a reversal of this pattern may be an early sign of inferior nerve damage. Comparisons of similar regions between eyes can also help identify diffuse loss of the RNFL. Unfortunately, the visibility of the RNFL is often difficult in the elderly, a high-risk population for glaucoma. This results from diffuse, physiological loss of optic nerve fibers, as well as an increasing opacity of the preretinal media. Table 12-2 presents a systematic approach for assessing the RNFL, which can be applied to direct clinical examination as well as photographs.

TABLE 12-2 SYSTEMATIC EXAMINATION OF THE RETINAL NERVE FIBER LAYER

Observe the general pattern of the RNFL approximately one disc diameter from the optic nerve head.

Compare the upper and lower nerve fiber bundles within each eye and between eyes.

Examine blood vessel coverage in the arcuate regions to estimate the degree of atrophy.

SPECIAL CONSIDERATION

The following situations may interfere with proper visualization of the retinal nerve fiber layer:

1. Advanced loss of nerve fibers due to other, coexistent eye disease
2. Media opacities that hamper visibility of the nerve fibers
3. A lightly pigmented fundus (e.g., myopia)
4. Poorly focused photographs

Several studies have shown that RNFL photography is superior to other methods of detecting glaucomatous optic nerve changes and their progression.¹⁴⁻¹⁶ Detectable RNFL abnormalities usually precede typical glaucomatous visual field loss as defined by conventional perimetric criteria.^{17,18}

Sommer et al.¹⁷ retrospectively examined sequential photographs of patients with increased intraocular pressure and found that RNFL abnormalities were the first observable changes in patients with glaucoma, and even preceded visual field damage by 6 years. Studies^{19,20} suggest that RNFL abnormalities are followed more closely by visual field defects obtained using the short-wavelength automated perimetry (SWAP), than those detected with conventional, white-on-white perimetry.

HIGH-TECHNOLOGY INSTRUMENTS

Although grading systems can help quantify RNFL abnormalities,^{10,11,21} the information from RNFL photography remains basically qualitative. New, objective, quantitative methods, such as nerve fiber layer polarimetry, ocular coherence tomography, and nerve fiber layer ophthalmoscopy, all offer the ability to record measurements and retrieve them for later comparison (Table 12-3). This feature gives all of these techniques the potential of providing longitudinal evaluation of the nerve fiber layer in clinical practice.

POLARIMETRY OF THE RETINAL NERVE FIBER LAYER

The nerve fiber analyzer (NFA) is a confocal scanning laser ophthalmoscope. It contains a modulator that polarizes a

Superior and inferior bundles more visible.
Look for slit and wedge defects.

Inferior bundles often thicker than superior.
Right and left eyes should be symmetrical.
Look for diffuse atrophy and hemiatrophy.

Look for cross-hatching of first- and second-order blood vessels by overlying RNFL.
Clear visibility of second-order vessels indicates severe atrophy.

TABLE 12-3 TECHNOLOGIES FOR MEASURING THE RETINAL NERVE FIBER LAYER

Technique	Principle
Nerve fiber layer polarimetry (Nerve Fiber Analyzer, GDx)	Measures change in the polarization state of polarized laser light induced by the birefringent properties of the nerve fiber layer.
Optical coherence tomography (OCT)	Determines time delays of reflected optical signals to identify natural tissue boundaries.
Scanning laser ophthalmoscopy [Heidelberg Retinal Tomograph, (HRT)]	Does not require a standard reference plane for the surface of the RNFL. Detects the surface of the RNFL by assembling multiple tomographic laser scans and determines its height by comparison to a standard reference plane.

780 nm laser beam, a device that compensates for polarization of the light by corneal fibers, and a polarization detector. This technique relies on the birefringent properties of the RNFL, which result from the fact that ganglion cell axons are composed of parallel microtubules with a diameter smaller than the wavelength of the light.²² This birefringence changes the state of polarization of a laser beam focused on the retina as it double-passes the RNFL. The change in the polarization state, called retardation, can be quantified by determining the phase shift between polarization of light returning from the eye with the known polarization of the illuminating laser beam.

A complete scan covers 256 × 256 individual retinal positions (pixels) in 0.7 seconds, and the field of view can be selected at 10, 15, or 20 degrees. After acquiring the data, the computer algorithm forms a color-coded retardation map by calculating the amount of retardation in degrees for each pixel within the field of view. Thus, retardation is a measure of relative, but not absolute, RNFL thickness. However, the retardation is unaffected by refractive errors, and this method does not depend on a reference plane or surface to determine the thickness of the RNFL.

In the NFA II and GDx, the standard color coding corresponds to a spectrum ranging from light yellow (thick RNFL) through orange, red, purple, and blue to black (absent RNFL). Figure 12–7A shows the analysis of a healthy subject, with the RNFL thicker in the region of the arcuate bundles, and thinner nasally and temporally. A glaucomatous eye (Fig. 12–7B) has a lower retardation in the affected RNFL, typically yielding retardation maps with less yellow and red.

To get an RNFL value, the operator chooses a desired location by moving a screen cursor on the image. For the quantitative analysis around the optic disc, typically at a diameter of 0.5 mm from the disc margin,²³ the software also displays the distribution of the RNFL retardation value along the circle and calculates the average nerve fiber layer retardation value along the entire circle, or in quadrants. Opening the circle and straightening it out produces a curve that typically contains a double hump, representing the superior and inferior arcuate bundles. The area under the curve (the integral) is also calculated to

present the cross-sectional area of nerve fiber tissue along the circle at the selected distance from the disc margin.

The NFA has undergone substantial improvement and is now a clinically useful tool for the detection of glaucoma.^{24,25} Although the earliest version of this instrument suffered from poor calibration and precision, the NFA II possesses a separate luminance detector to automatically adjust the intensity setting of the retardation measurements, thus reducing dependence on input from the operator.²⁶ A newly developed software algorithm in the NFA II and GDx allows reliable detection of blood vessels from the reflectance image. This permits the operator to disregard the noisy retardation data related to the blood vessels in any later computations. The latest version, the GDx, contains a large normative database and a statistical software package for comparing an individual's data with those of age-matched normal subjects of the same ethnic origin.

One weakness of this instrument has been that it assumed, and compensated for, a standard birefringence for all corneas. The recent version of the GDx will allow the operator to customize this compensation for individual patients. This will greatly minimize the effects of corneal birefringence and improve detection of meaningful nerve fiber measurements.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a noninvasive, noncontact technique for imaging the retina. Imaging with OCT (Zeiss-Humphrey, San Leandro, California) resembles an ultrasound B-scan in that it extracts distance information from the time delays of reflected signals. However, using optical rather than acoustic waves, OCT improves depth resolution 10-fold. The resulting direct, cross-sectional imaging of the retinal anatomy provides objective, quantitative measurement of nerve fiber layer thickness and appears to improve early diagnosis and sensitive monitoring of a variety of retinal and optic nerve head diseases, including glaucoma.^{27–30}

Measurements are performed using a fiberoptic, integrated Michelson interferometer with a short-coherence-length, superluminescent diode light source. Combined

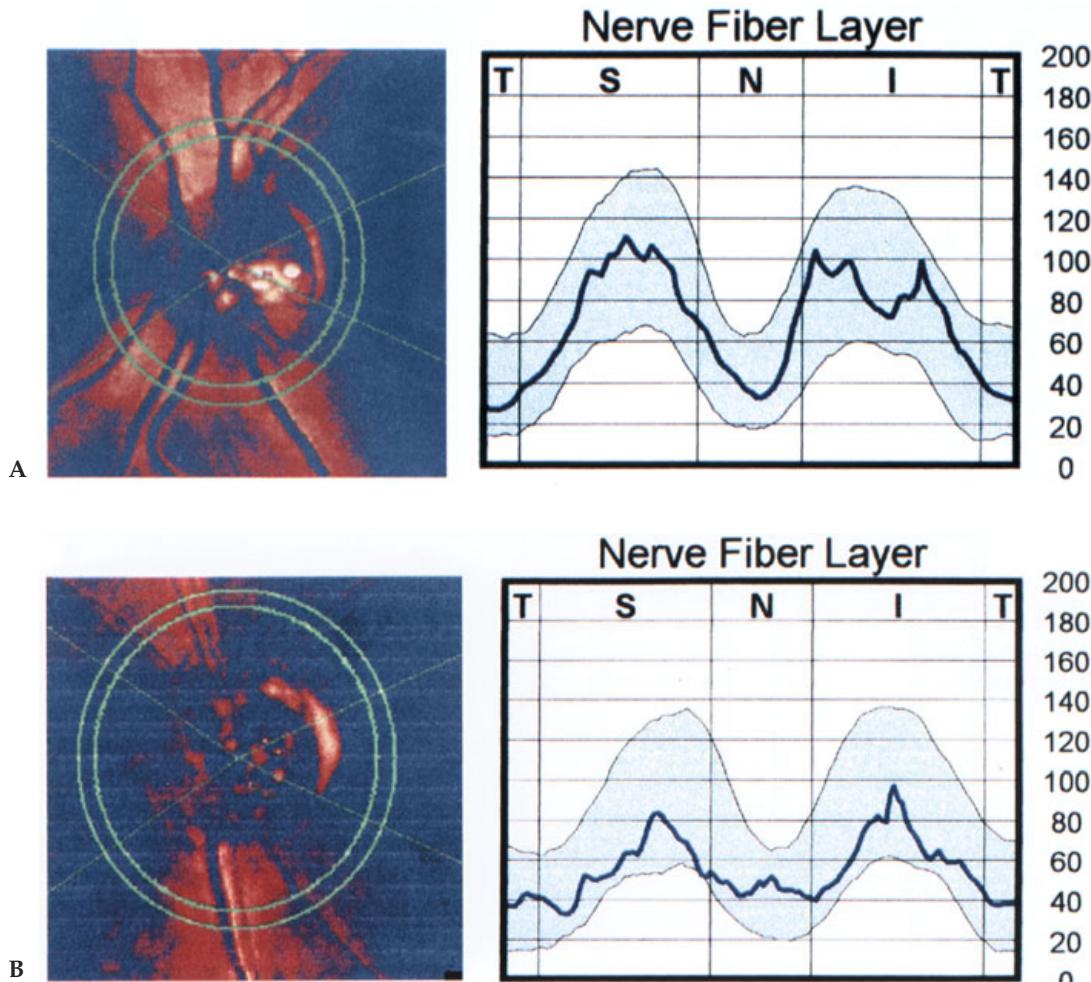


FIGURE 12-7 The Nerve Fiber Analyzer (NFA). (A) Color coded image of the optic disc and the peripapillary retinal nerve fiber layer (RNFL) of a healthy, nonglaucomatous 30-year-old individual taken with the NFA. The graph on the right shows the RNFL profile around the optic disc with the typical, double hump pattern. (B) An NFA image of a 60-year-old patient with glaucoma and a deep scotoma in the inferior visual field. Note the altered RNFL profile. (Courtesy of professor Albert Alm, Uppsala, Sweden.)

with a standard slit-lamp biomicroscope, the OCT instrument uses a +78-diopter condensing lens to visualize the fundus and deliver the probe beam onto the retina in various scanning patterns, such as circular or radial scans in selected locations and angles on the retina. An infrared video camera demonstrates the position of the OCT scan on the retina, and a computer monitor displays the corresponding OCT image in real time. The optic disc and fundus vessels can be used as landmarks to direct the scans to the RNFL abnormalities visible on the digital images.

A digitized image of 512 (transverse) by 1024 (axial) pixels is obtained in 1 second with a resolution of 8–10 μm in a false-color scale that represents the intensity of tissue reflectance.²⁷ Measurements of retinal thickness are obtained automatically by a computer algorithm that searches for reflectivity changes observed at natural boundaries within the retina. These boundaries can be overlaid on a false-color display of each image to allow the operator to assess the quality of the fit.

Cross-sectional OCT images of the retina are constructed from the backscattering information provided by 512 individual longitudinal A-scans (Fig. 12-8A,B).²⁷ In practice, the transverse resolution is limited by the spacing between adjacent A-scans on the retina. Schuman et al., testing different diameters, selected a circle diameter of 3.4 mm as standard for future studies.³⁰ They found that the mean RNFL thickness along this circle was 285 μm in their normal subjects and 261 μm in patients with glaucoma.

The image of 3.4-mm-diameter circular scan may also be useful in identifying generalized RNFL thinning as compared with healthy eyes. In fact, measurement of RNFL thickness with the OCT in glaucoma patients and normals compares favorably with clinical scoring of red-free photographs and visual field loss.^{30a} This is an important advance because identifying diffuse RNFL thinning in clinical practice is particularly difficult. However, localized drop-out of axons in glaucoma is not infrequent. In these cases, defective areas appear in OCT as areas of

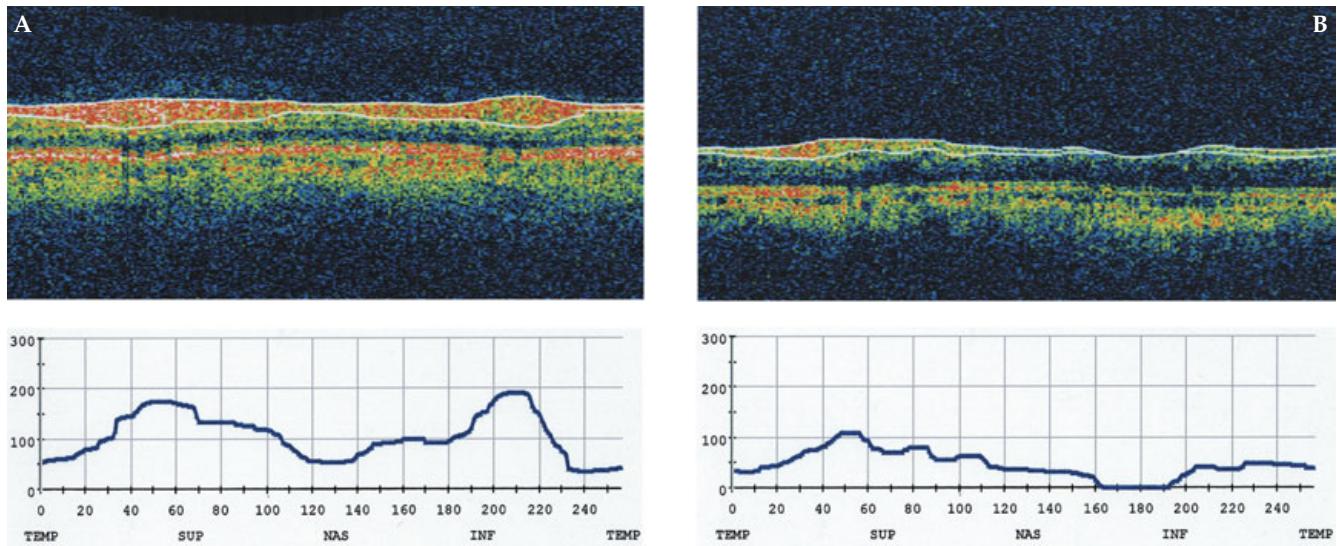


FIGURE 12-8 Optical coherence tomography. (A) Fundus image (above) taken with OCT3, using the fast circular scan, and graphical representation of the nerve fiber layer thickness (below) in a normal eye (A) and an eye with glaucoma (B). The fast circular scan acquires 256 A-scans per image, and acquires three scans in rapid sequence, taking a total time of 1.5 seconds. The data from the three scans are averaged to produce mean parameters. The layer color-coded red (between the anterior white lines) indicates a thick and healthy nerve fiber layer in the normal eye. In the patient with glaucoma there is almost complete loss of the retinal nerve fiber layer, particularly inferiorly, indicating severe glaucomatous damage.

reduced backscattering as compared with the adjacent normal RNFL. These localized RNFL defects can progress in depth as well as in width over time.

However, a 3.4-mm-diameter circular tomogram contains 512 pixels spaced approximately 110 μm apart. With a circular scan, the probability of correctly identifying wedge-shaped local changes may be diminished because the measurement points are too few and far between. Directing the OCT scans to areas where damage is documented or suspected using other clinical methods should increase the ability of this instrument to determine subtle changes in RNFL thickness. Increasing the number of longitudinal scans and reducing the scanning time should make the device more suitable for detecting and quantitating small defects of the RNFL. In fact, the recently released OCT3 has increased the number of scanned points by a factor of five, without an increase in scanning time. In addition, the axial resolution has been enhanced by approximately 20%.

PITFALL... Increased circle diameters and longer linear scans, which both increase spacing between measurement points, may limit the potential of optical coherence tomography to detect localized retinal nerve fiber layer defects.

that acquires, records, and analyzes three-dimensional topography of the optic nerve in a rapid, patient-friendly, accurate, and reproducible manner that does not require dilation of the pupil.³¹⁻³⁶ Using a 670 nm diode laser light source, this instrument acquires the image as a series of optical section images at 32 consecutive focal planes. From the mean image of three scans taken during a single session, this instrument calculates a large number of topographic parameters that describe the optic nerve head topography. These are discussed in detail in Chapter 11.

This device also determines the height of the RNFL in relation to a topographic reference plane. This plane currently is set 50 μm posterior to the mean contour line height at the papillomacular nerve fiber bundles, which changes very little or not at all during the development and progression of glaucoma. Using this region also minimizes the range of possible location changes because the RNFL at the papillomacular bundle is only 50 μm thick, as compared with the upper and lower arcuate areas, where RNFL thickness can be as high as 300 μm .³ Using this reference plane, this instrument measures and calculates two RNFL parameters from the peripapillary region. The mean RNFL thickness (mRNFLt) is the reference height minus the mean height of the measured contour, whereas the RNFL cross-section area (RNFLcsa) represents the mRNFLt multiplied by the length of the contour line (Fig. 12-9A,B).

Although localized RNFL defects can be easily seen on the real time monitor display during confocal scanning, the computed average images may not reflect these RNFL defects. Therefore, as with the GDx and

SCANNING LASER OPHTHALMOSCOPY

The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany) is an automated, digital image acquisition and analysis system

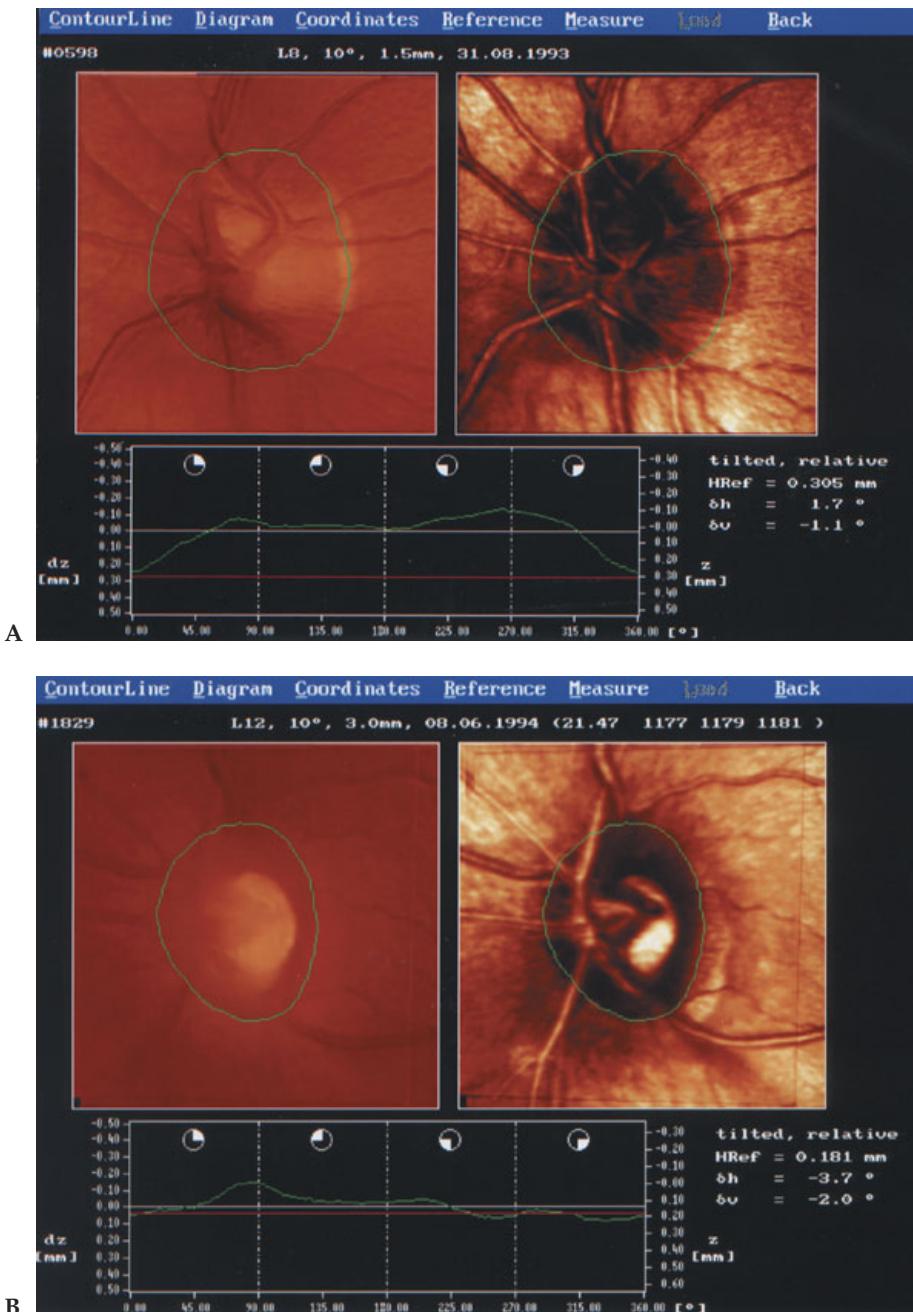


FIGURE 12-9 Heidelberg Retinal Tomography (HRT). (A) Topographic (left) and reflectance (right) images of a normal optic disc. The green contour line, which indicates the disc margin, has been drawn manually. In the graph, the contour line indicates the profile of the neural tissue along this contour line. The double hump indicates the thicker nerve fiber layer in the superior and inferior poles of the optic disc. The distance between the green contour line and the red reference level indicates the thickness of the retinal nerve fiber layer (RNFL) in each location. The area between the lines indicates the RNFL cross-section area at the disc edge. (B) An HRT image of a glaucomatous eye shows optic disc cupping and an RNFL defect at the 5 o'clock position. The inferior RNFL hump has disappeared, indicating neural tissue damage.

OCT, the HRT may be most effective when used to study optical sections over the damaged area or region in question.³⁷ The visual display of the double hump RNFL pattern with this device may provide a more sensitive, although less quantitative, assessment of focal RNFL thinning.

DETECTING GLAUCOMATOUS DAMAGE

Glaucoma frequently produces clinically detectable tissue damage in the optic nerve head and the RNFL. Several studies have found a close relationship between structural changes of the RNFL and the optic nerve head in glauco-

matous eyes.³⁸⁻⁴⁰ Although most new technologies concentrate on assessing changes at the optic nerve head, those that allow measurement of the RNFL next to the optic disc offer several potential advantages.

Compared with the optic nerve head, axons in the retina are spread out in a thin layer. This suggests that examination of the RNFL will be more sensitive to minor losses of axons than evaluating the optic nerve head. In addition, the nerve fiber pattern is very little influenced by the anatomy of the scleral canal and the optic nerve head. This minimizes inter and intra-individual variation in the arrangement and pattern of nerve fibers, thus improving the chance of detecting pathological abnormalities.

However, the number of fibers in the normal population varies widely,^{41–43} and this severely limits our ability to use assessment of the peripapillary RNFL to differentiate between normal and glaucomatous eyes. Moreover, in the early stages of glaucoma, RNFL defects may be poorly seen near the optic disc because undamaged, more proximally originating axons cover the defect, leaving the surface topography of the RNFL relatively unchanged. Furthermore, these techniques allow only a small field of view. For these reasons, RNFL photographs, and possibly the recently introduced retinal thickness analyzer (RTA), may be more suitable for screening purposes.⁴⁴

As with optic nerve head imaging devices, the greatest potential of these methods for analyzing the RNFL may lie in their ability to assess its changes over time, particularly when combined with increasingly powerful computers that allow data storage and sophisticated comparison algorithms. Technology advances should continue to decrease the cost of these digital systems and increase their use. Regardless of how advanced these technologies become, final diagnostic and therapeutic decisions will always involve informed, careful clinical judgment.

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PERIMETRY

Chris Johnson, Ph.D.

Tests that determine optic nerve function are critical to the diagnosis and management of glaucoma. Perimetry and visual field testing have been the most widely developed of these tests, and include suprathreshold static perimetry, kinetic perimetry and automated static perimetry, the current “gold standard” for clinical assessment of visual function in glaucoma. Characteristic defects in the visual field typically reflect the anatomy of the nerve fiber layer and often lead to the diagnosis of glaucoma, particularly when correlated with physical evidence of glaucomatous optic neuropathy. We now rely heavily on automated perimetry to quantify the extent of injury and detect disease progression.

However, new perimetric test procedures and methods of analyzing and interpreting results are constantly being developed and refined, with the goals of increasing test sensitivity and reliability, and reducing test time and patient fatigue. These tests include the Swedish Interactive Testing Algorithm, Short Wavelength Automated Perimetry, Frequency Doubling Technology Perimetry, and High Pass Resolution Perimetry. As we improve our understanding of the capabilities and limitations of these different approaches, the tests that are useful will gradually be incorporated into the routine clinical management of glaucoma patients.

PERIMETRY

Assessing visual function in glaucoma patients has traditionally relied on evaluating the peripheral visual field, and perimetry plays a critical role in glaucoma management. Perimetry can detect early losses in sensitivity produced by glaucomatous damage, often before the patient notes any changes in vision. In addition, because the pattern of glaucomatous visual field loss is usually distinct, it can often help differentiate glaucoma from other causes of optic

nerve damage. Although monitoring visual function over time to determine the effectiveness of therapy is perhaps the most important role of visual field testing in glaucoma, identifying progressive visual field loss is often difficult and generally requires correlation with other clinical findings.

This chapter reviews perimetry as applied to glaucoma, with particular emphasis on automated static perimetry, currently the most prevalent clinical visual field test. More comprehensive discussions of perimetry and related test procedures appear in several excellent reference sources.^{1–6} However, personal experience in correlating visual field results with other clinical findings provides the best appreciation of how perimetry helps us manage patients with glaucoma.

THE PSYCHOPHYSICAL BASIS FOR PERIMETRY

Conventional perimetry relies on the psychophysical concept of the increment threshold, or differential light threshold. This is the minimum amount of light (ΔL) needed to make a stimulus just detectable on a uniform background (L). Under typical perimetric and visual field testing conditions (a low photopic adaptation level), $\Delta L/L$ is constant (Weber’s Law).^{7,8} Thus, factors that affect the amount of light reaching the retina (changes in pupil size, ocular media opacities, etc.) will affect the stimulus and the background equally, thereby maintaining a constant $\Delta L/L$ relationship, and decreasing variability. Both static and kinetic perimetry measure the differential light threshold at representative locations throughout the visual field. In suprathreshold static perimetry, stimulus presentations are set a predetermined amount above the normal differential light threshold for these various visual field locations.

Automated static perimetry usually characterizes results in terms of visual sensitivity, which is the reciprocal of the

TABLE 13-1 THE RELATIONSHIP BETWEEN SENSITIVITY IN DECIBELS (dB) AND STIMULUS LUMINANCE IN APOSTILBS (asb) AND CANDELAS PER SQUARE METER (cd/m^2) ON THE HUMPHREY FIELD ANALYZER

Sensitivity (dB)	Stimulus Luminance (asb)	Stimulus Luminance (cd/m^2)
0	10,000	3,175
10	1000	318
20	100	31.8
30	10	3.18

differential light threshold (sensitivity = 1/threshold). A low-increment threshold indicates high sensitivity, and vice versa. For automated perimetry, sensitivity is expressed in decibels (dB). The decibel scale, based on logarithmic intervals, is relative and uses, for reference, the most intense stimulus that the perimeter can provide. This is defined as 0 dB. Table 13-1 presents the relationship between sensitivity and stimulus luminance for the Humphrey Field Analyzer. Unfortunately, because various perimeters may have different maximum stimulus intensities and background adaptation levels, dB values may be quite different from one device to another, making direct comparisons very difficult.

Manual kinetic perimetry specifies isopters and scotomas in terms of the size and luminance of the stimulus presented. The first character, a roman numeral (0 through V), indicates the size of the stimulus, as indicated in Table 13-2. This notation for target size is also used to specify target size in automated static perimetry. The second character is a slash, followed by a number (1 through 4) and a lowercase letter (a through e). The numbers and lowercase letters correspond to 0.5-log-unit (5 dB) and 0.1-log-unit (1 dB) changes in stimulus luminance, respectively, as indicated in Table 13-3. In his original determinations, Goldmann found that a 0.5-log-unit decrease in stimulus luminance roughly compensates for a 0.6-log-unit increase in stimulus area. Therefore, a II/4e stimulus is approximately

TABLE 13-2 SIZE OF TARGETS FOR THE GOLDMANN PERIMETER

Goldmann Size	Stimulus Area (mm^2)	Average Diameter (degrees)
0	0.0625	0.05
I	0.25	0.11
II	1	0.22
III	4	0.43
IV	16	0.86
V	64	1.72

as detectable as a III/3e stimulus. In comparison to automated static perimetry, a III/4e stimulus on the Goldmann perimeter corresponds to a 10 dB stimulus, and the V/4e stimulus represents the closest approximation to a 0 dB stimulus for automated static perimetry. With a reliable patient and appropriate testing, the results for static and kinetic perimetry generally compare well.

Because we can generally detect a moving stimulus better than a stationary one, static and kinetic perimetry occasionally produce quite different results. This "stato-kinetic dissociation" most frequently appears in optic neuritis and related optic neuropathies, as well as in some cortical disorders.⁹⁻¹² In glaucoma, however, static and kinetic perimetry results are usually reasonably consistent.

In the normal eye, the differential light sensitivity varies with location in the visual field. Typically, sensitivity is greatest at fixation (representing the fovea) and decreases progressively for more eccentric locations. Figure 13-1A illustrates, in three dimensions, the visual field sensitivity, or "hill of vision," for a left eye. The peak of the hill of vision is the location of the fovea, and the small but deep depression to the left of the foveal peak is the blind spot, corresponding to the location of the optic nerve head, which lacks photoreceptors. Note that the normal visual field extends farther temporally than it does nasally and farther inferiorly than it does superiorly, giving it an oval, conical appearance when viewed in three dimensions.

Automated static perimetry usually presents the visual field in a gray-scale format, where lighter areas denote regions of high sensitivity and darker areas lower sensitivity (Fig. 13-1B). In contrast, kinetic perimetry represents the visual field in a manner similar to a topographic map. Here, isopters, which indicate areas of equal sensitivity around the visual field for specific targets, and scotomas, or localized areas of reduced sensitivity, define the contours of the visual field (Fig. 13-1C).

TABLE 13-3 STIMULUS LUMINANCE FOR THE GOLDMANN PERIMETER (LOWER SETTINGS FOR LEVELS 2, 3, AND 4 ARE NOT INCLUDED)

Filter Setting	Luminance (apostilbs)	Log Luminance
1a	13	1.1
1b	16	1.2
1c	20	1.3
1d	25	1.4
1e	32	1.5
2e	100	2.0
3e	320	2.5
4e	1000	3.0

PEARL... Interpreting visual field tests involves detecting sensitivity deficits, determining which result from visual system pathology,¹ and then diagnosing the nature of this pathology.¹

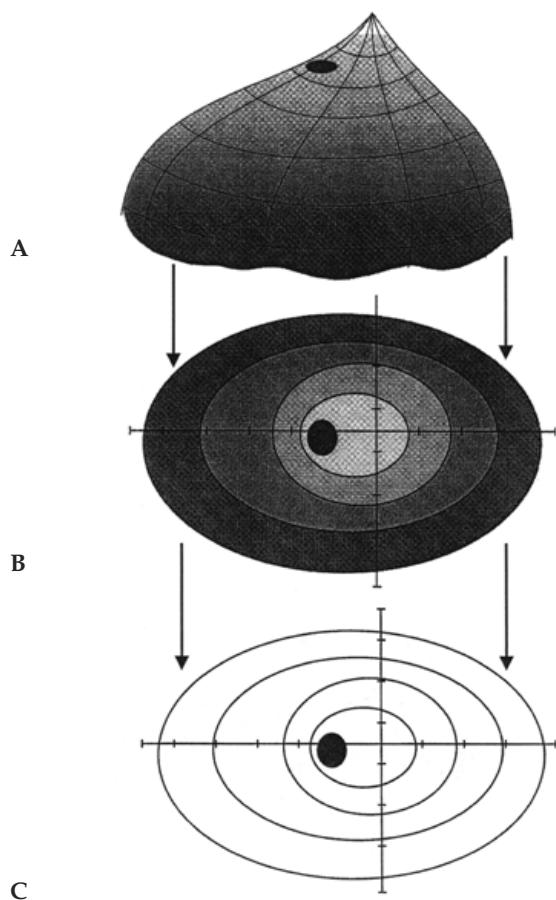


FIGURE 13-1 (A) Three-dimensional representation of the sensitivity of the eye to light (the “hill of vision”) for a left eye. (B) Gray scale representation of the hill of vision, as used in automated static perimetry. (C) Isopter and scotoma representation of the hill of vision, as used in manual kinetic perimetry.

Interpreting visual field tests involves detecting sensitivity deficits, determining which result from visual system pathology, and then diagnosing the nature of this pathology. Although separating real from artifactual deficits requires familiarity with perimetry testing methods and potential sources of error, determining the true underlying pathology demands close correlation of the

location of the functional defect with clinical examination of the visual system, particularly the optic nerve and retina. These functional and structural correlations include recognizing that the inferior visual field projects to the superior retina, and the superior visual field to the inferior retina. Similar, inverse projections also occur for the nasal and temporal visual fields.

Perimetry uses differential light sensitivity as a non-invasive probe for evaluating functional loss. Because it is impractical to evaluate every small region of the field of view, perimetric tests sample regions with the highest chance of undergoing pathological change. Thus most automated procedures will concentrate on the central 30 degrees of the visual field because this is where the vast majority of initial glaucomatous field deficits occur. Although perimetry procedures are subjective and require good patient cooperation, they can successfully evaluate and monitor visual function in the majority of glaucoma patients.

METHODS OF PERFORMING PERIMETRY AND VISUAL FIELD TESTING

Perimetrists have developed many methods for examining the visual field over the past two centuries. Although all forms of visual field testing examine one eye at a time, each has its strengths and weaknesses, and no single procedure can satisfy the visual field evaluation needs of all patients. Table 13-4 lists the major advantages and disadvantages of each technique.

SUPRATHRESHOLD STATIC PERIMETRY

Suprathreshold static perimetry is best suited for rapid screening of the visual field. While presenting stimuli at key locations, the examiner determines if the patient can see the targets at each location. Numerous suprathreshold static perimetry tests exist.^{1,13,14} The simplest is the confrontation field, with the examiner determining if a patient can see common objects such as fingers, pencils, tongue depressors, or medicine bottle caps, in different locations of the peripheral visual field. This examination is

TABLE 13-4 ADVANTAGES AND DISADVANTAGES OF DIFFERENT TYPES OF PERIMETRY

	<i>Advantages</i>	<i>Disadvantages</i>
Suprathreshold static	A rapid test procedure. Easier for patients to do.	Limited quantitative information available. Difficult to follow patients to evaluate progression.
Kinetic	A more flexible test procedure. Tests the entire peripheral visual field.	Limited normative data. Results are dependent on perimetrist technique.
Static	Uses standardized procedures. Normative database available. Statistical analysis packages.	Demanding and inflexible for patients. Typically only the central visual field is tested.

quick, easy, and adaptable to virtually any environment. However, confrontation visual fields can only detect gross visual field loss and will miss subtle deficits, such as those present in early glaucoma.

The tangent screen and Goldmann perimeter can also perform suprathreshold static visual field testing. The Armaly-Drance procedure, one of the most useful manual suprathreshold static screening techniques for glaucoma, checks for early nasal steps, and deficits in the paracentral visual field out to 30 degrees' eccentricity. This procedure, also available on many automated perimeters, is described in detail by Anderson.¹

Automated perimeters offer several rapid suprathreshold static visual field screening test procedures, in addition to the Armaly-Drance technique. Although these tests use many different strategies,^{1,13,14} they all present suprathreshold stimuli that should be easily detected by someone with normal peripheral vision. The luminance of the initial stimulus originates either from normal population characteristics (e.g., stimuli that can be seen by 99% of the normal population) or from testing the patient at one or two locations that are unlikely to be affected by pathology (e.g., temporal to the blind spot). The latter procedure carries a distinct risk of overlooking diffuse loss because it will adjust stimuli to levels that match the patient's general threshold. For example, a sensitivity loss of 4 dB throughout the visual field will also reduce the suprathreshold targets, causing the screening procedure to miss the generalized depression.

Most suprathreshold static perimetric procedures attempt to reduce the occurrence of false-negative errors by noting stimuli that are not seen and presenting them again later in the test at the same intensity. The printed test results use unique symbols to indicate the locations where targets were, and were not, seen. In some instances, if the subject misses a stimulus initially, the test will present two or more brighter targets at the same location to determine the severity of the deficit. When this occurs, the printout uses symbols of different sizes or shapes to display the extent of sensitivity loss.

Figure 13–2 presents the results of a 120-point full visual field screening procedure performed on the Humphrey Field Analyzer. Open circles indicate where stimuli were seen, filled squares show the location of undetected stimuli, and a triangle represents the blind spot. This representation clearly displays the location of affected and unaffected regions and illustrates the pattern of visual field loss.

Although suprathreshold static perimetry is fast and easy to perform, it provides only limited understanding of the patient's visual field. With recent developments of new, faster threshold estimation procedures, such as the Swedish Interactive Testing Algorithm (SITA),^{15–17} the time-saving advantages of suprathreshold screening examinations become less important in deciding which visual field test to use.

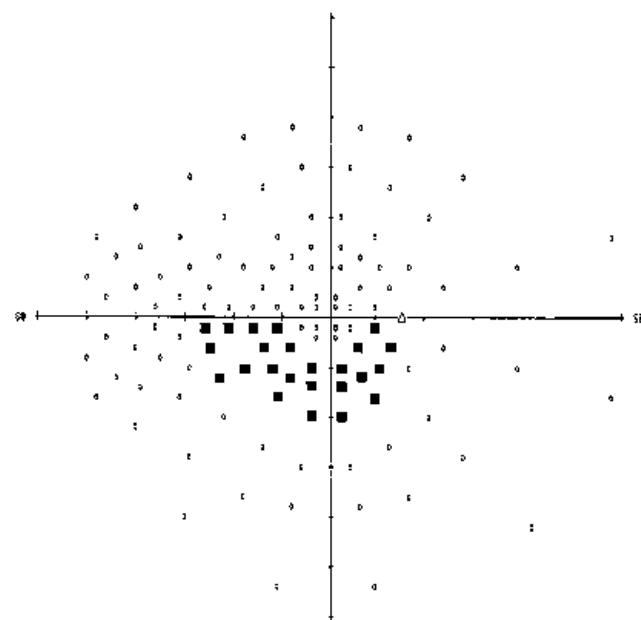


FIGURE 13-2 An example of the test results produced by suprathreshold static perimetry, showing an inferior arcuate scotoma using the Humphrey Field Analyzer 120-point full visual field screening test.

MANUAL KINETIC PERIMETRY

Manual kinetic perimetry is an interactive, flexible test that can be used to evaluate patients unable to comply with the rigors of automated perimetry. In addition, Goldmann perimetry permits evaluation of the entire peripheral field out to 90 degrees, and may offer more information than static perimetry, particularly in patients with extensive loss of the central 30 degrees of the visual field. Many clinicians still feel that Goldmann kinetic perimetry results are easier to interpret than automated static perimetry results, provide a better characterization of the pattern of visual field loss, and yield more useful information in cases of advanced visual field damage. Performed by a skilled perimetrist, kinetic visual field testing is both accurate and extremely efficient.

However, manual kinetic perimetry is highly examiner-dependent and lacks standardized test procedures.^{1,18} This hinders the detection of subtle deviations from normal values, especially in patients with generalized or widespread loss. Also, this test is becoming a lost art because training a high-quality manual kinetic perimetrist is time-consuming and demanding, particularly when compared with teaching automated perimetry.

Kinetic perimetry uses a moving (approximately 4 to 5 degrees per second¹⁹) stimulus of fixed size and luminance to map out areas in which stimuli are seen (isopters) and not seen (scotomas). As the patient fixates steadily on a central target, the examiner moves the stimulus from the far periphery toward fixation until the patient indicates (usually by pressing a response button) that it is visible. By

noting these locations and repeating the process at different meridians around the field of vision, the examiner “maps” an isopter, or contour line of equal sensitivity, for that particular stimulus. Departures from the expected position and shape of normal isopters are explored and mapped by sampling between the original meridia using similar kinetic scans. When different target sizes and luminances are used, this process creates several isopters, equivalent to a two-dimensional topographic representation of the hill of vision (see Fig. 13–1C). Sensitivity losses due to visual system pathology can manifest either as generalized depression, with overall shrinkage of the isopters, or as localized damage, which produces regional indentation and deformation of isopters.

Between isopters, spot checks with appropriate stimuli are used to detect small areas of sensitivity loss (scotomas).

Using stimuli of varying intensity or size to map such scotomas from the center outward in all directions (in a manner opposite to the plotting of isopters), the examiner can define their depth and contour. Generally, mapping isopters and scotomas for an adequate evaluation of the full visual field requires a minimum of 4 to 5 stimuli. Anderson has provided an excellent discussion of manual kinetic perimetry techniques using the Goldmann perimeter.¹

Figure 13–3A,B presents localized and advanced glaucomatous visual field deficits, as determined on the Goldmann perimeter. The areas of visual field loss are easily seen in the displacement of isopters from their normal oval shape and the presence of scotomas, the solid or cross-hatched areas.

Most deficits in patients with early-to-moderate glaucomatous visual field loss occur within the central

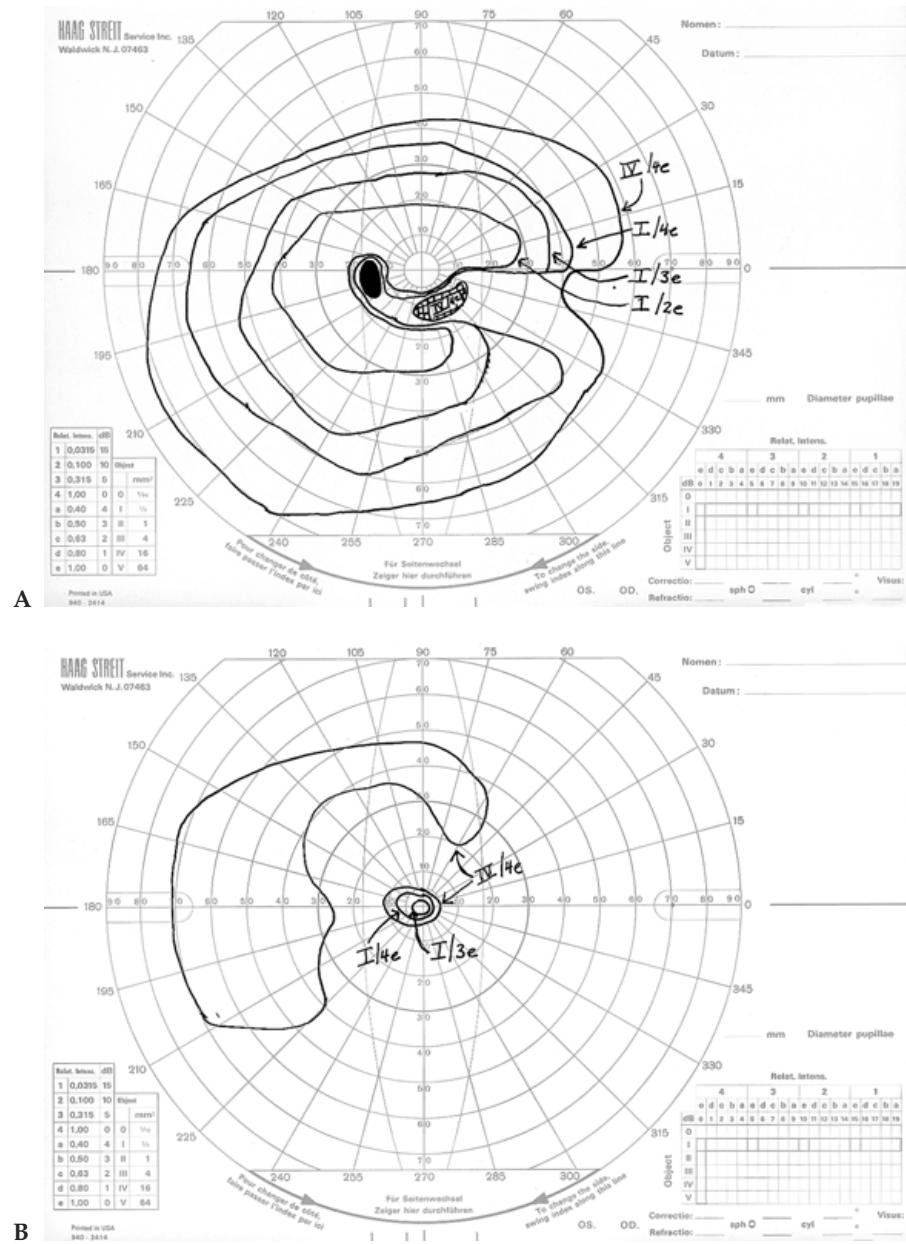


FIGURE 13-3 (A) Localized inferior arcuate and (B) advanced glaucomatous visual field defects in the left eye, as determined by Goldmann kinetic perimetry. Note the large temporal island beyond 30 degrees' eccentricity in (B).

30 degrees. (Fig. 13–3A). In more advanced cases, the field loss can encompass most of the central 30 degrees and extend to the far periphery. Figure 13–3B presents a case of advanced glaucoma in which the visual field is reduced to only a small, 5-degree central island and a larger, temporal region. A central 30-degree test would miss the large temporal visual field, information that could be used to determine if patients with advanced glaucomatous damage are progressing, and to assess their mobility capabilities.

AUTOMATED STATIC PERIMETRY

Automated static perimetry is now the standard clinical method of assessing the visual field. Its advantages include (1) the ability to provide consistent, standardized test procedures over time and among different clinics; (2) the ability to immediately compare test results to age-matched normative data and perform extensive statistical evaluation of test results; (3) the ability to store and quantitatively compare multiple test results obtained at different times; and (4) the ability to combine test results obtained at different locations to perform multicenter clinical trials.

PITFALL... Automated static perimetry is not “automatic.” The examiner must carefully monitor alignment and attention level and remain in communication with the patient throughout the test.²

Despite its name, automated static perimetry is not “automatic”; the examiner cannot assume that the computer will take care of everything. Automated visual field tests are time-consuming, demanding, and often boring. Patients can become misaligned, fall asleep, or daydream, and may require frequent rest breaks. Others feel uncomfortable and anxious if left alone in a darkened room. To avoid these problems, the examiner must carefully monitor alignment and attention level and maintain rapport with the patient throughout the test.

Automated static perimetry presents stationary targets at fixed, predetermined locations in the visual field, usually in a grid pattern that straddles the horizontal and vertical meridians. Stimuli appear in a pseudorandom order to minimize anticipatory eye movements by the patient, using the staircase or bracketing procedure to determine the differential light sensitivity at each location. A stimulus, once detected, is presented later in the same location at a lower luminance. If this is not detected, its luminance is increased for the next presentation. The extent of luminance increase or decrease becomes smaller with each change in direction of the staircase until a minimum step size is reached. A predetermined number of reversals in staircase direction usually generates sufficient information to calculate an estimate of the differential or increment threshold at each location. For the Humphrey Full Threshold test, a threshold is determined by 2 reversals using 2 dB steps. The “fast” version of this program

uses a single reversal in 3 dB steps. While faster than the full threshold test, it is generally considered to be less reliable for ongoing monitoring of glaucoma patients.

The standard procedure for automated perimetry uses a size III target and a 30-2 stimulus presentation pattern (a 6-degree grid of points within the central 30 degrees, bracketing the horizontal and vertical meridians), as shown in Figure 13–4. Many clinicians now use the 24-2 stimulus presentation pattern, which is identical to the 30-2 pattern, except that the outer rim of test points has been removed except for the two outermost test locations adjacent to the nasal horizontal meridian. It has 54 test locations instead of the 76 locations in the 30-2 test and is about four minutes faster. The main disadvantage is that in a small percentage of cases, peripheral defects may be missed or may be more difficult to interpret than with the 30-2 pattern.

Another stimulus presentation, the central 10-2 pattern, presents a dense grid of points with 2-degree spacing over the central 10 degrees. This test procedure is most useful for patients with end-stage glaucoma and only a small central island remaining, or in cases with visual field loss encroaching upon fixation. The size V target offers another option for testing glaucoma patients with advanced visual field loss. Because it will be detected by more visual field locations, this target provides more visual field locations to monitor than the size III target.

INTERPRETING VISUAL FIELD INFORMATION

This discussion will concentrate on full threshold testing for the Humphrey Field Analyzer, but most of it also applies to the increasingly popular SITA, discussed at the end of this section. Several excellent texts on perimetry and visual field testing interpret the results of suprathreshold static screening procedures and manual kinetic perimetry,^{1–8,20} although these skills are best acquired through clinical experience.

SINGLE VISUAL FIELD ANALYSIS

Accurate interpretation of the full threshold 30-2 visual field test requires close attention to all parts of the visual field printout, illustrated in Figure 13–4. The top portion contains information about the patient: pupil size, visual acuity, and refractive correction, all of which help determine that the proper test procedure and conditions were utilized. Small pupils (less than 2 or 3 mm in diameter) and improper lens corrections can produce artifactual test results that sometimes mimic pathological sensitivity changes.

PEARL... Informed and accurate interpretation of visual fields depends on careful consideration of all the information in the visual field printout. No portion should be attended to the exclusion of others.

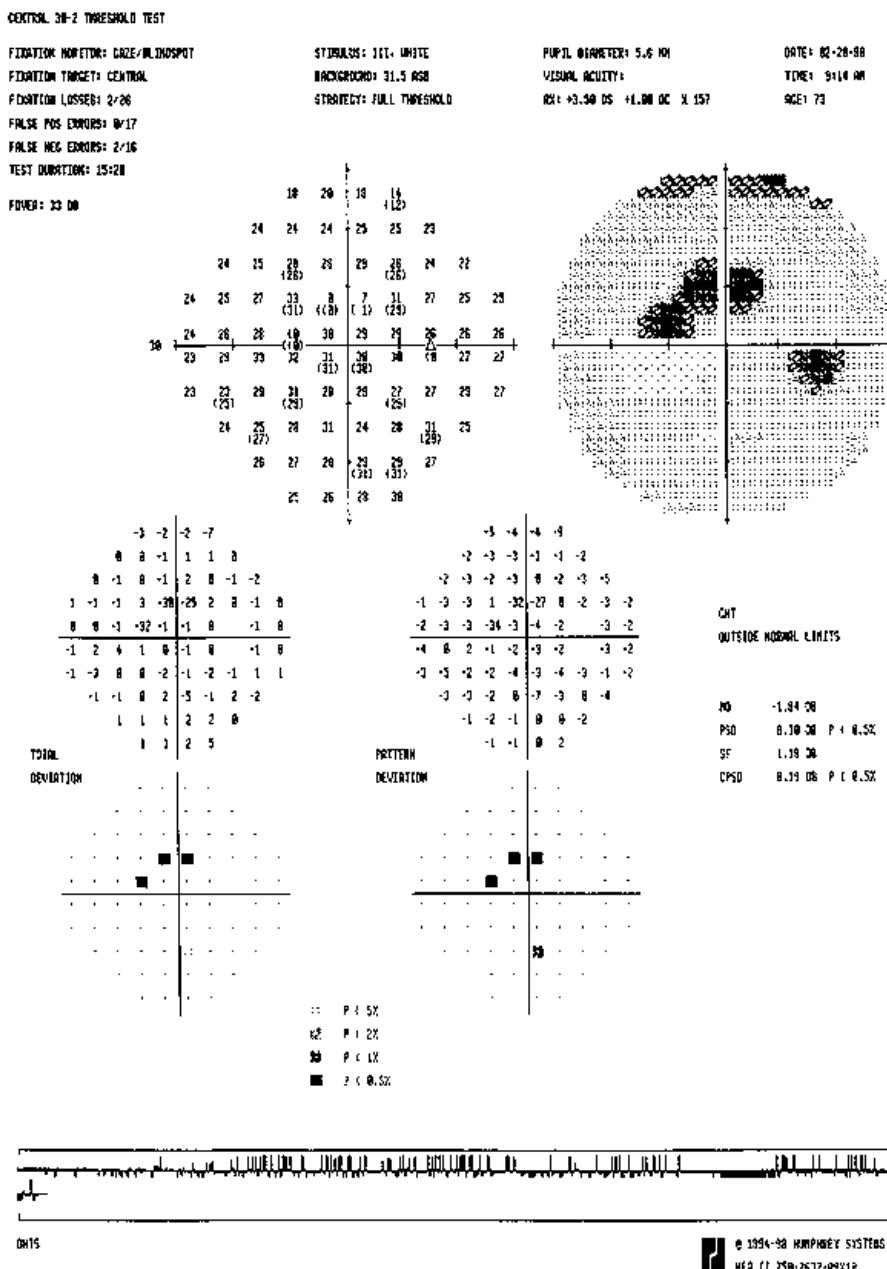


FIGURE 13-4 An example of the printed output for automated static perimetry of a right eye using a full threshold 30-2 test procedure conducted on the Humphrey Field Analyzer Model 750.

The top portion also contains reliability indices, such as false-negative and -positive responses and fixation losses. False-negative responses are checked by presenting stimuli at particular visual field locations 9 dB brighter than the previously determined detection thresholds. Failure to respond indicates that the patient may be daydreaming or is about to fall asleep. However, patients with more extensive visual field sensitivity loss often exhibit higher variability in the most affected visual field areas, which, if greater than 10 dB, can produce a higher number of false-negative responses. If the patient misses more than 33% of the false-negative stimulus presentations, this is considered outside normal limits, and two Xs appear beside the false-negative index, along with a "Low Patient Reliability" warning.

To check false-positive responses, the program includes stimulus intervals without presenting a target and records the number of times that the patient responds during these intervals. This helps identify the "trigger happy" patient. Again, a value of greater than 33% false-positive responses is considered to be outside normal limits, resulting in two Xs beside the false-positive index and the "Low Patient Reliability" warning. On the Humphrey Field Analyzer II Model 750, some tests evaluate false-positives by examining all of the intervals between stimulus presentations and patient responses. They then calculate the false-positive rate from the percentage of time that the response button was pressed when no targets were being presented.

Fixation losses are monitored by intermittently projecting a stimulus in the location of the blind spot and

determining whether or not the patient responds. A patient who sees the blind spot stimulus may be making eye movements and not maintaining fixation. Fixation losses in more than 20% of blind spot checks will also generate the Xs and a "Low Patient Reliability" warning.

PITFALL... Excessive fixation losses are by far the most common cause of a "Low Patient Reliability" warning. Although some of these cases truly result from poor patient fixation, others do not.

The Humphrey Field Analyzer begins every test by plotting the location of the blind spot. Therefore, patients unfamiliar with automated perimetry or not fully prepared to begin the test may not properly localize their own blind spot. This can result in excessive fixation losses as the blind spot is rechecked throughout the test.

The Humphrey Field Analyzer attempts to minimize this problem by presenting many fixation loss trials during the first 60 to 90 seconds of testing. If it detects greater than 33% fixation losses during this time period, it produces several beeps. This should prompt the examiner to pause and replot the blind spot, which usually corrects the problem. If excessive fixation losses still occur, the examiner should observe the eye directly to determine whether the patient is fixating steadily or looking around. Several multicenter clinical trials and research investigations have shown that most patients can perform reliable visual fields when carefully tested and appropriately monitored.^{20–22}

The patient's visual sensitivity for the fovea appears immediately below the reliability indices, along with any symbols denoting a foveal threshold that is beyond the normal 5, 2, 1, or 0.5% probability levels. The foveal sensitivity, in conjunction with visual acuity, can help assess the possible influence of ocular media opacities or whether a visual field defect is encroaching on fixation.

The patient's visual sensitivity plotted at each field location appears below and to the right of the foveal sensitivity, with numerical values (dB of sensitivity) on the left and a graphic gray scale representation on the right. The gray scale indicates areas of high sensitivity with light shading, and progressively lower sensitivities with darker shadings. This provides a more rapid "Gestalt" of the pattern of visual field sensitivity than is possible from simply examining the numerical sensitivity values. Most practitioners find that this gray scale representation combined with the Total and Pattern Deviation probability plots (described in the following text) is the most helpful in diagnosing patterns of visual field loss due to glaucoma and other ocular diseases.

The visual field indices, which are general summary statistics generated for the visual field, appear below the gray scale representation. Each is compared to a database for the age-adjusted normal population to determine

whether the patient's values are within normal limits, or outside normal limits at the 5, 2, 1, or 0.5% probability levels. Mean deviation (MD) represents the average deviation from normal age-adjusted sensitivity values exhibited by all of the test locations evaluated in the test procedure. A negative value indicates that the patient's overall visual field sensitivity is lower than average for a normal observer of the same age, whereas a positive value means that the patient's overall visual field sensitivity is better than average. Thus MD provides an index of the patient's visual field as a whole.

Pattern standard deviation (PSD) analyzes the shape of the patient's visual field, looking for local irregularities as compared with the normal field, which slopes smoothly from the fovea out to 30 degrees' eccentricity. Using the MD to account for any general, widespread sensitivity differences, this index adjusts the patient's entire visual field to the level of the normal field and then evaluates the amount of irregularity or local deviation from normal. Localized scotomas produce significant departures from the normal slope and increase the value for PSD. The PSD index provides an indication of the amount of localized visual field sensitivity loss, such as is seen in glaucoma patients.

Short-term fluctuation (SF) indicates the amount of variability exhibited by the patient during the test procedure. It is determined by performing a second threshold determination at 10 preselected visual field locations and calculating the average variation of the repeated measures for these points. Corrected PSD (CPSD) recalculates the PSD value, adjusting for the patient's SF.

All four indices are compared with the normal distributions for each of these values to determine whether they are within normal limits or beyond normal at the 5, 2, 1, or 0.5% probability levels.⁶

The total deviation and pattern deviation probability plots are some of the most useful information provided in the printed test results. The total deviation plot compares the patient's sensitivity at each visual field location to the average sensitivity of a normal subject of the same age. The numerical values indicate the amount by which the patient's sensitivity at each point is higher (positive numbers) or lower (negative numbers) than the average sensitivity for age-adjusted normal individuals. Below the numerical values, another plot indicates locations that have sensitivity within normal limits (single dot) or sensitivity outside the normal with a 5% (light stippling), 2% (intermediate stippling), 1% (heavy stippling), or 0.5% (solid black) probability that this value differed from normal by chance alone. This provides an immediate indication of the visual field locations with abnormal sensitivity and an approximation of the severity of the abnormality.

The pattern deviation probability plot is similar to the total deviation plot, except that it adjusts the height of the visual field to compensate for any generalized or diffuse sensitivity loss (or gain) in order to better define localized

visual field sensitivity deficits. This is accomplished by using the sensitivity corresponding to the 85th percentile (seventh-most-sensitive visual field location) to adjust the overall height of the visual field. For example, if a patient's seventh-most-sensitive visual field location is 2 dB below the seventh-most-sensitive point in the age-adjusted normative database, all of the total deviation scores are adjusted upward by 2 dB to create the pattern deviation probability values.

By comparing the total deviation and pattern deviation probability plots, one can determine the amount of diffuse and localized sensitivity loss. A diffuse sensitivity deficit will produce probability symbols on the total deviation plot, but none on the pattern deviation plot

(Fig. 13–5A). If the sensitivity deficit is predominantly localized, then the total deviation and pattern deviation probability plots will look essentially identical (Fig. 13–5B). Combinations of diffuse and localized sensitivity losses will produce intermediate results where some, but not all, of the total deviation probability symbols appear on the pattern deviation plot (Fig. 13–5C). The appearance of probability symbols on the pattern deviation plot despite a completely normal total deviation probability usually indicates a "trigger-happy" patient, with physiologically impossible sensitivity values (50 dB or higher) and excessive false-positive errors (Fig. 13–5D).

The Humphrey Field Analyzer II Model 750 uses infrared reflections from the eye to objectively "track" its

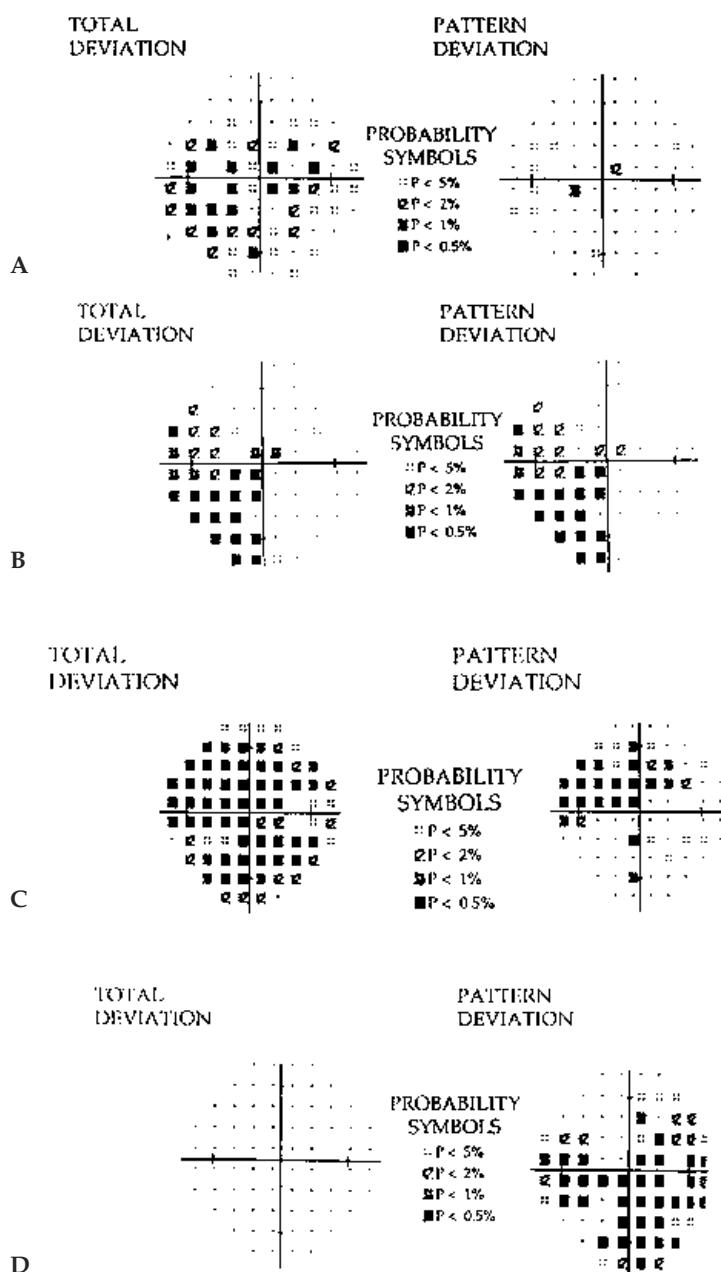


FIGURE 13-5 A comparison of total deviation and pattern deviation probability plots for (A) predominantly widespread or generalized (diffuse) sensitivity loss, (B) predominantly localized sensitivity loss, (C) a combination of widespread and localized sensitivity loss, and (D) a "trigger happy" patient, who even presses the button when targets are not detected.

position during testing and presents a chronological record of eye position at the very bottom of the printout. With stable fixation, the record approximates a single thin horizontal line, whereas erratic fixation results in larger and more frequent departures from this line. In Figure 13-4, the printout shows that fixation was quite good throughout the first part of the test procedure but became more variable toward the end.

PATTERNS OF GLAUCOMATOUS VISUAL FIELD LOSS

The patterns of localized visual field loss that most commonly occur in glaucoma closely reflect the underlying anatomy of the nerve fiber layer and pathophysiology of glaucoma. Retinal ganglion cell nerve fibers, or axons, enter the optic nerve head in three very distinct patterns (Fig. 13-6). One group, the papillomacular bundle, has the shape of a candle flame and enters the temporal side of the optic nerve head. These fibers serve the macular region and locations between the optic disc and the fovea. Approximately 60 to 70% of all of the retinal ganglion cell nerve fibers lie within the papillomacular bundle.

Radially arranged fibers entering the nasal aspect of the optic nerve head originate from ganglion cells in the peripheral nasal retina and serve the temporal visual field. A third set of nerve fibers joins the top and bottom of the optic nerve head, fanning out in an arcuate pattern above and below the papillomacular bundle. Temporal to the macula, these superior and inferior fibers

remain separated and form a distinct horizontal raphe. Axons from ganglion cells that lie above the horizontal raphe always enter the superior pole of the optic nerve head, and vice versa.

Arcuate nerve fiber bundles entering the top and bottom of the optic nerve head are apparently more susceptible to the initial glaucomatous insult, and many of the initial defects that occur in glaucoma reflect damage to these fibers. A common deficit in early glaucoma is the nasal “step,” so named because of a distinct sensitivity transition that “respects” the horizontal midline in the nasal visual field (Fig. 13-7A,B).

PEARL... The anatomy of retinal ganglion cell nerve fibers is of interest because most glaucoma visual field deficits mimic pathophysiological damage to these bundles of fibers.

Other common deficits in early-to-moderate glaucoma include a paracentral scotoma, which can appear as either an extension of the blind spot (Fig. 13-7C), an isolated defect in the arcuate nerve fiber bundle region approximately 15 degrees from fixation (Fig. 13-7D), or the more common full arcuate nerve fiber bundle defect (Fig. 13-7E). Less commonly, glaucoma produces a temporal wedge deficit by damaging the radially oriented nerve fibers that enter the nasal optic disc (Fig. 13-7F). Although glaucoma occasionally causes a diffuse depression of sensitivity or widespread visual field loss, small pupils, mild cataract, and fatigue can also produce these results.

PEARL... Although a generalized depression in sensitivity can result from glaucoma, it should be considered nonspecific because other factors, such as small pupils, cataract, and fatigue, can also produce this result.

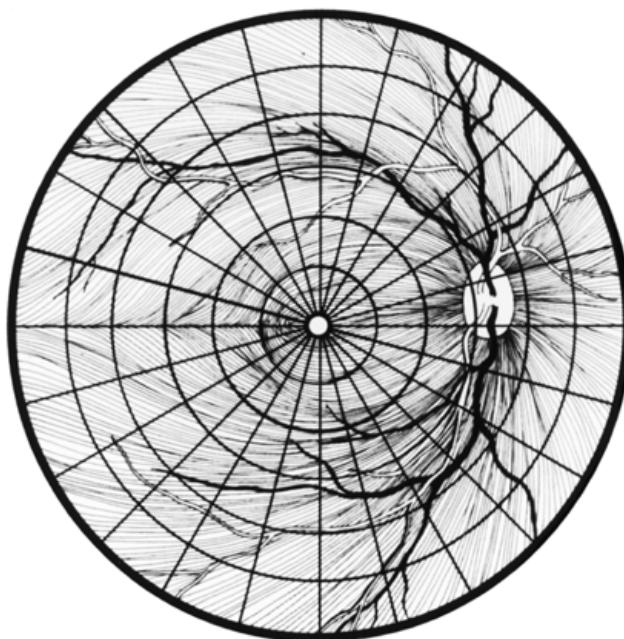


FIGURE 13-6 Schematic representation of the nerve fiber bundles and the vascular arcade as they enter the optic nerve head in a right eye, superimposed on the Goldmann visual field plot.

Several simple clinical pearls, based on the anatomy of the arcuate nerve fiber layer, can help identify visual field losses consistent with glaucoma. First and foremost is the appearance of the nasal step, as already described. Second, the long axis of defects in the arcuate nerve fiber bundle region often orient, or “point,” toward the blind spot. Finally, in addition to their distinct arcuate shape, nerve fiber bundle defects tend to “fan out” from the blind spot, appearing narrower near the blind spot and wider as they approach the nasal horizontal meridian.

Once detected, the pattern of glaucomatous visual field loss generally correlates well with the appearance of the optic nerve head and the retinal nerve fiber layers (Fig. 13-8A,B). Lack of such correlation should suggest other fundus pathology. Several retinal and optic nerve

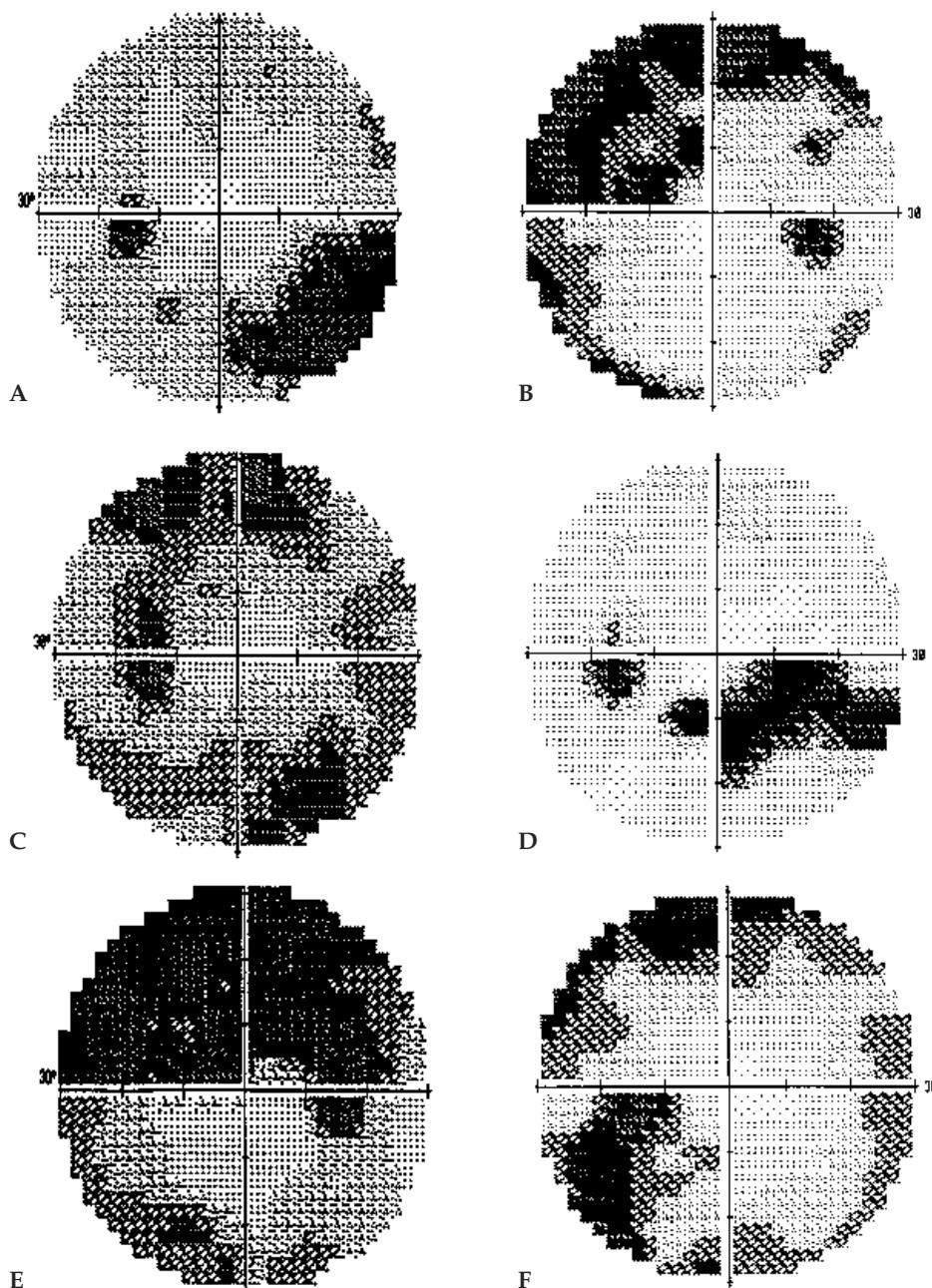
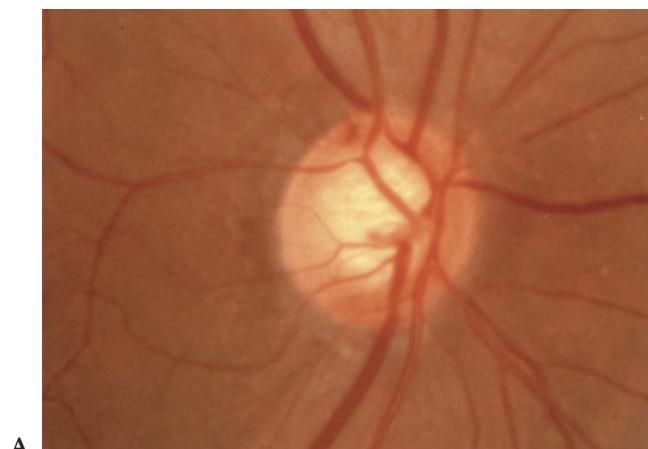


FIGURE 13-7 Typical visual field defects associated with glaucomatous damage. (A) Inferior nasal step, (B) superior nasal step, (C) paracentral scotoma extending from the blind spot, (D) partial arcuate nerve fiber bundle defect, (E) full arcuate nerve fiber bundle defect, and (F) a temporal wedge defect.

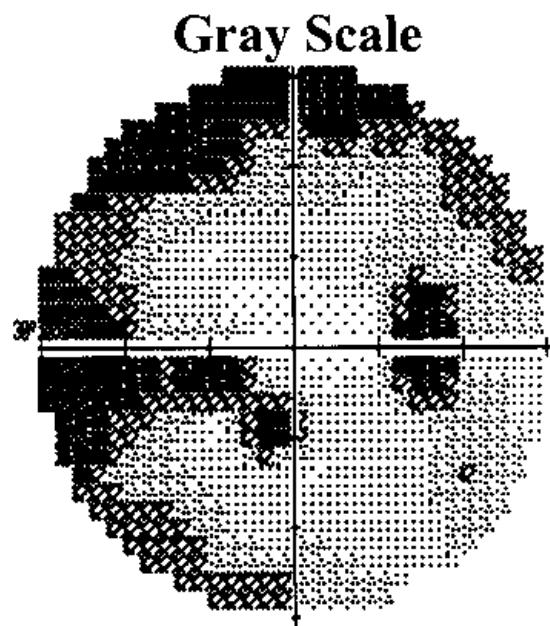
diseases can mimic glaucomatous visual field defects, including branch artery occlusions, chorioretinal scars, optic neuritis, optic nerve head drusen, and others. Figure 13-9 presents an example of a chorioretinal scar in the superior arcuate nerve fiber bundle and its corresponding inferior visual field deficit.

In spite of our best treatments, some patients with glaucoma undergo progressive visual field loss (Fig. 13-10). Although large visual field changes are readily distinguished, most patients undergo more subtle changes, and loss of sensitivity must always be differentiated from variability from one test to another.

Glaucomatous visual field loss often begins as a subtle peripheral nasal step, or as a small superior or inferior paracentral scotoma in the arcuate nerve fiber bundle regions. This typically expands into a partial, and then a full, arcuate scotoma from the blind spot to the nasal horizontal meridian. In the majority of cases, the initial glaucomatous visual field loss resides in either the superior or the inferior hemifield. In fact, a sensitive indicator of early glaucomatous visual field loss, the Glaucoma Hemifield Test, takes advantage of this by evaluating the asymmetry in sensitivity for mirror image nerve fiber bundle regions across the horizontal midline.



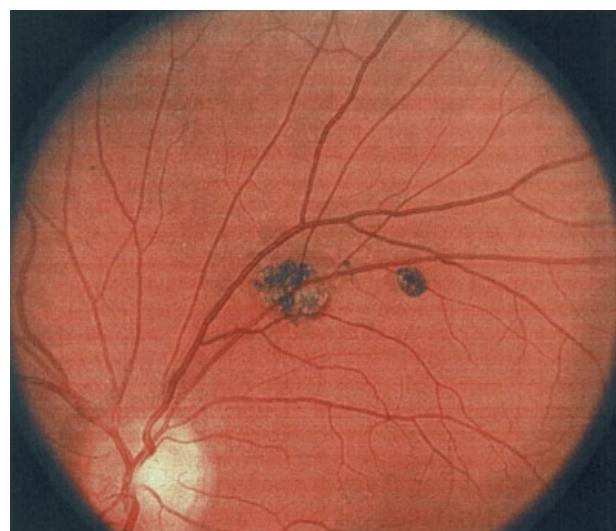
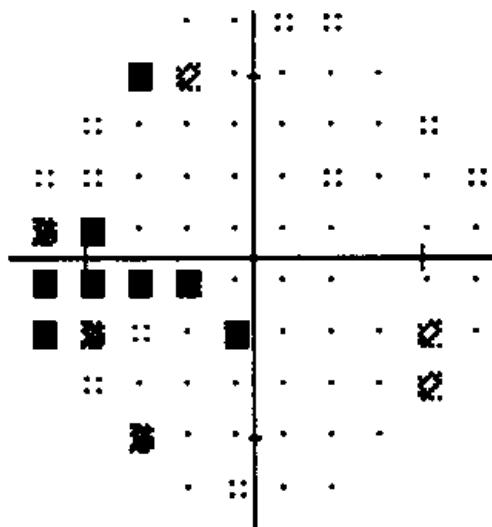
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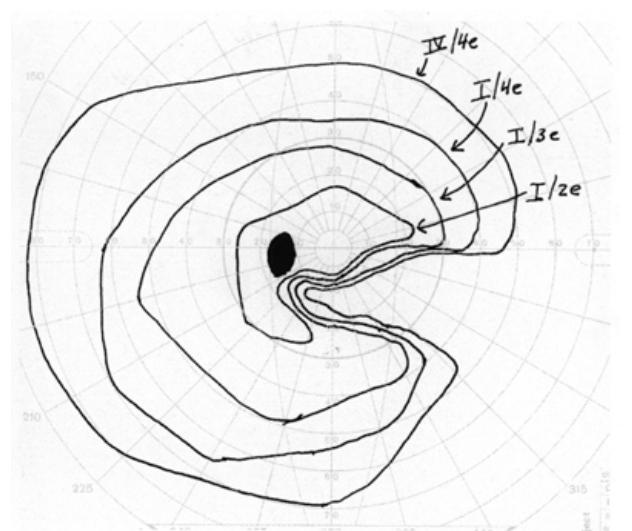
B

FIGURE 13-8 An example of the right optic nerve head of a patient with normal-tension glaucoma. (A) The optic disc photo reveals a small splinter hemorrhage and a notch at the 11 o'clock position. (B) The visual field shows an inferior nasal step corresponding to the area of involvement in the optic nerve.

Pattern Deviation



A



B

FIGURE 13-9 (A) An example of a chorioretinal scar in the superior nerve fiber bundle and (B) the corresponding inferior visual field.

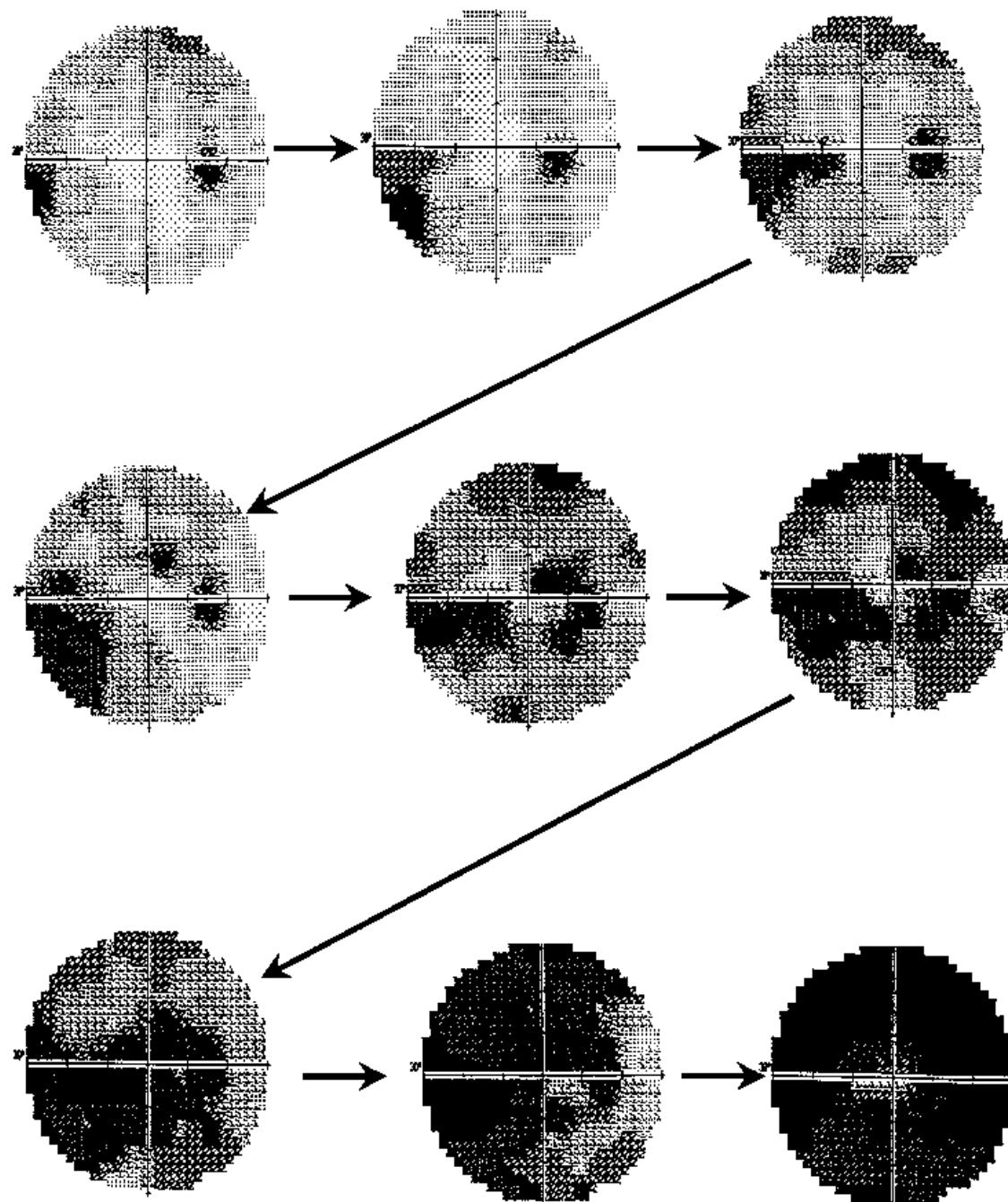


FIGURE 13-10 An example of typical glaucomatous visual field progression, proceeding from an early nasal step (upper left) and to end-stage glaucoma (lower right).

As visual field loss progresses to a full arcuate defect, losses in the opposite hemifield often appear. The full arcuate defect eventually “breaks through” to the periphery, a result of damage to fibers progressively more peripheral to the arcuate bundles, until it involves the extreme nasal field and that above or below the central 30 degrees. In advanced glaucomatous injury, the most commonly used automated perimetry tests,

which extend only to the central 24 or 30 degrees of the visual field, will not record the full extent of visual field damage.

Progression continues in both hemifields until the final stages of glaucomatous damage, when only a small central island of vision remains, often with a second island of vision in the far temporal visual field. Although a test procedure that concentrates on the central 10 degrees

with a finer grid of test points can help monitor the former, the latter may only appear on a Goldmann visual field.

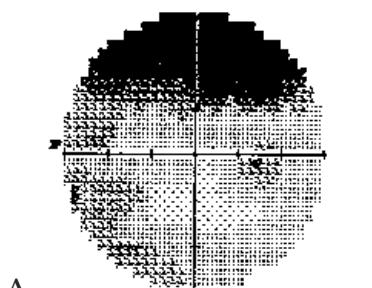
ARTIFACTUAL TEST RESULTS

Many factors can produce artifactual test results. A droopy eyelid can create a superior visual field depression, which resembles a partial superior nerve fiber bundle-type defect (Fig. 13–11A). Using surgical tape can help keep the eyelid from obstructing the superior visual field, yet permits the patient to blink and remain comfortable during testing.

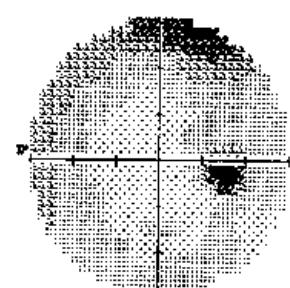
PITFALL... Artifactual test results can arise from a variety of factors, including ptosis, poor positioning of the trial lens, inaccurate refractive correction, and small pupils.

Figure 13–11B shows a trial lens rim artifact and its disappearance upon retesting. Trial lens rim artifacts can be produced by improper lens positioning and a tendency for some patients to back away from the perimeter bowl.²³

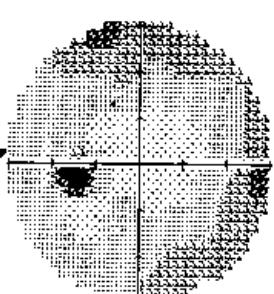
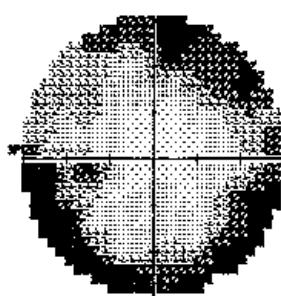
Artifactual test results can also result from using the wrong lens correction. The proper lens is based on the



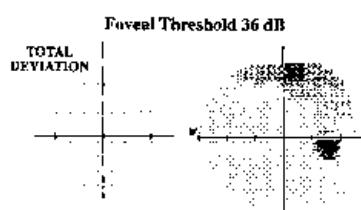
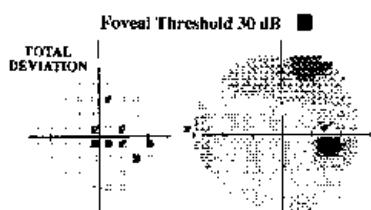
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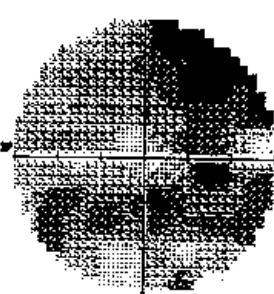
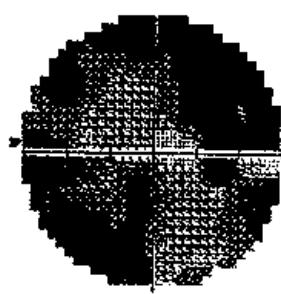
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C



C



D

FIGURE 13-11 Artifactual visual field test results. (A) Superior visual field depression due to ptosis (left) and improvement after taping eyelid up (right). (B) Trial lens rim artifact (left) and its disappearance following proper alignment of the lens holder (right). (C) Central visual field depression due to the use of an incorrect trial lens (left) and its disappearance after the proper lens correction was used (right). (D) Visual field determined with the pupil diameter at 1 mm (left) and 7 mm (right).

patient's distance correction and adding the appropriate near correction for the testing distance of 30 cm, as dictated by the patient's age (Fig. 13–11C). Small pupils (less than 2 mm in diameter) can greatly restrict the amount of light reaching the retina. This can cause the adaptation state to fall below a photopic level, where Weber's Law no longer pertains, and can significantly alter the apparent visual field sensitivity (Fig. 13–11D).

DETECTING PROGRESSION OF GLAUCOMATOUS VISUAL FIELD LOSS

Determining whether a patient's visual field has improved, deteriorated, or remained stable over time remains the greatest challenge in visual field interpretation and a fundamental consideration in the management of glaucoma. Several clinical trials have found that distinguishing true glaucomatous change from random variability requires multiple confirming visual fields.^{24–26} This was shown by the Ocular Hypertension Treatment Study (OHTS), where 88% of initial glaucomatous visual field deficits were not validated on a repeat visual field examination.²⁴ Because sequences of any two visual fields within the same patient can indicate worsening, recovery, or stability, the full chronological set of visual fields must be considered to best identify long-term trends.

PITFALL... Long-term trends are best appreciated by examining the patient's full chronological set of visual fields, rather than simply comparing the two most recent fields to each other.

Several tools can help determine whether or not a glaucoma patient's visual field is stable.^{1,6} The first is a simple overview analysis printout, which chronologically summarizes the patient's performance over time, including the gray scale; numerical, total, and pattern deviation plots for each visual field; test date; reliability indices; and visual field indices (Fig. 13–12). A welcome alternative to arranging a series of single field analysis printouts on the table or floor, this overview provides an easy means of detecting general trends in visual field sensitivity.

The change analysis, shown in Figure 13–13, provides a summary comparison for up to 16 visual fields obtained at different times. The box plots at the top summarize the deviations from normal for all locations represented in the total deviation probability plot. The three horizontal bars in the middle of the box plot indicate the median deviation from normal (the 50th percentile). The top and bottom of the box indicate the deviations from normal for the locations corresponding to the 15th and 85th percentiles, and the I-bars above and below the box show the deviations for the visual field locations with the best and worst sensitivity. Graphical plots of each of the visual field indices are also presented for successive examinations,

along with an indication of the slope of a least squares linear regression for MD.

The glaucoma change probability analysis averages two visual field tests to establish a baseline sensitivity against which subsequent visual fields are compared to determine whether there has been improvement, no change, or progression at each location in the visual field (Fig. 13–14). This determination is based on the variability characteristics of glaucoma patients who were tested repeatedly over a 1-month period of time and were unlikely to undergo actual glaucomatous visual field changes. Locations with changes from baseline greater than the variability demonstrated by those stable glaucoma patients are denoted by open triangles for improved areas and solid triangles for areas that became worse.

SWEDISH INTERACTIVE TESTING ALGORITHM

Automated static perimetry has traditionally relied on a bracketing or staircase procedure, already described, to estimate sensitivity at each visual field location. Unfortunately, these techniques can be tedious and highly variable. The Swedish Interactive Test Algorithm (SITA) was developed for the Humphrey Field Analyzer to reduce test time and improve the reliability of visual field sensitivity measures.^{15–17}

Unlike traditional staircase procedures, SITA continuously updates its estimate of sensitivity measures during the test using a maximum likelihood approach. Prior to testing, SITA uses a priori knowledge to construct models of normal and glaucomatous visual fields. The models contain information about age-corrected normal visual thresholds at each test point, frequency-of-seeing curves, and how these characteristics at different test point locations correlate with each other. The frequency-of-seeing curves help define the sensitivity threshold at each location, whereas the slope estimates variability. Steep slopes suggest low variability and shallow slopes high variability.

The test begins by determining the threshold at four primary points, one in each quadrant, similar to the conventional full threshold procedure. Using the a priori knowledge of the frequency of seeing curves, stimuli are then presented at each test location as close to the threshold intensity as possible. At each test location, the patient's response is used to refine these curves at the tested location as well as at adjacent locations, and those in the related arcuate nerve fiber bundle pattern, since these are characteristic of glaucomatous visual field loss. By continually refining these curves, SITA maximizes the accuracy of stimulus presentations and minimizes the total presentations required to determine the sensitivity threshold, defined by satisfying a predetermined level of variability. This thresholding strategy, along with modifying the determination of false-positive errors and eliminating the determination of short-term fluctuation (which was found to have a negligible effect) is responsible for the significant time savings of this test.

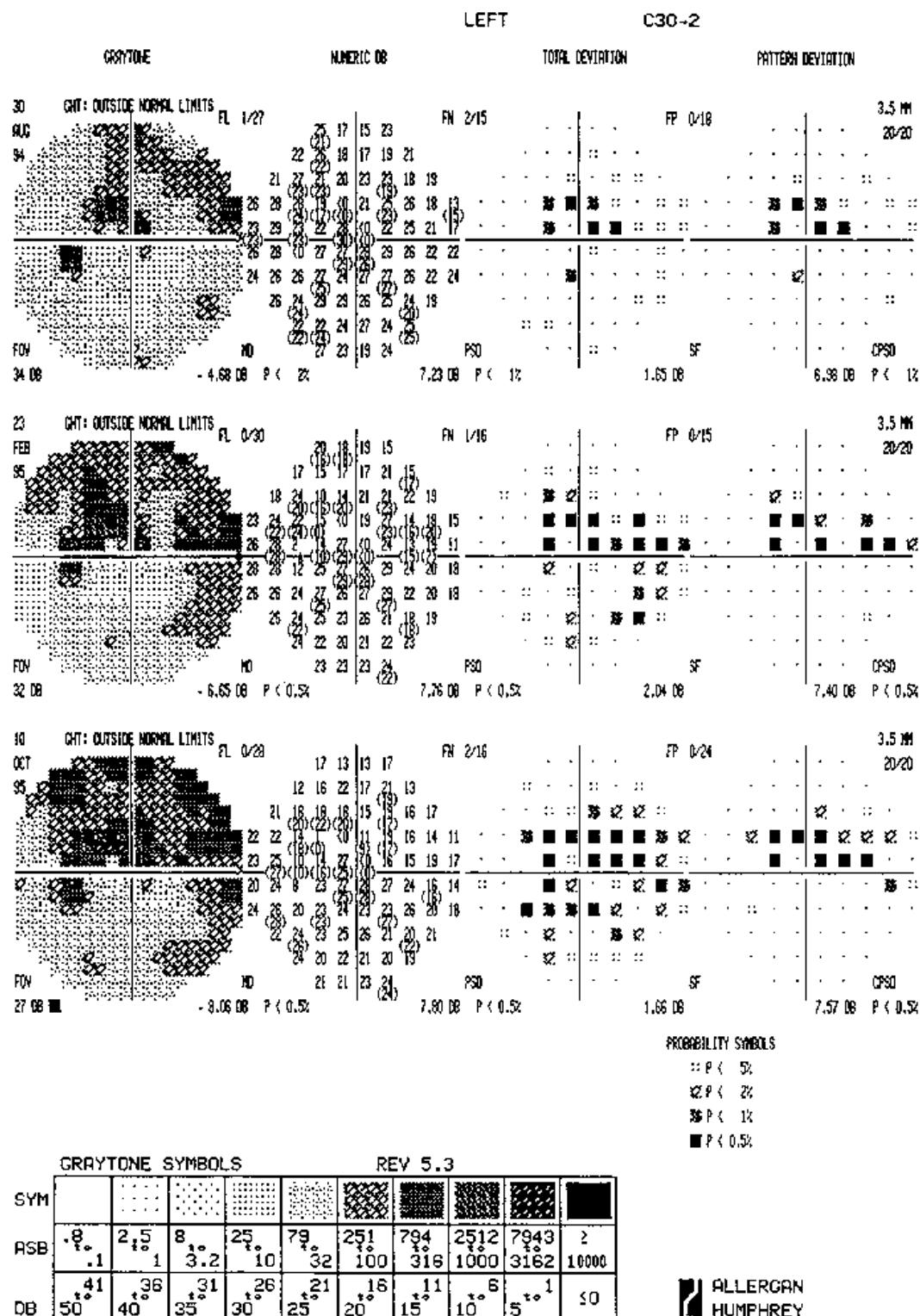


FIGURE 13-12 An example of the overview analysis printout for the Humphrey Field Analyzer showing glaucomatous progression. Gray scale, numeric, total, and pattern deviation plots are shown, along with the values of the visual field and reliability indices.

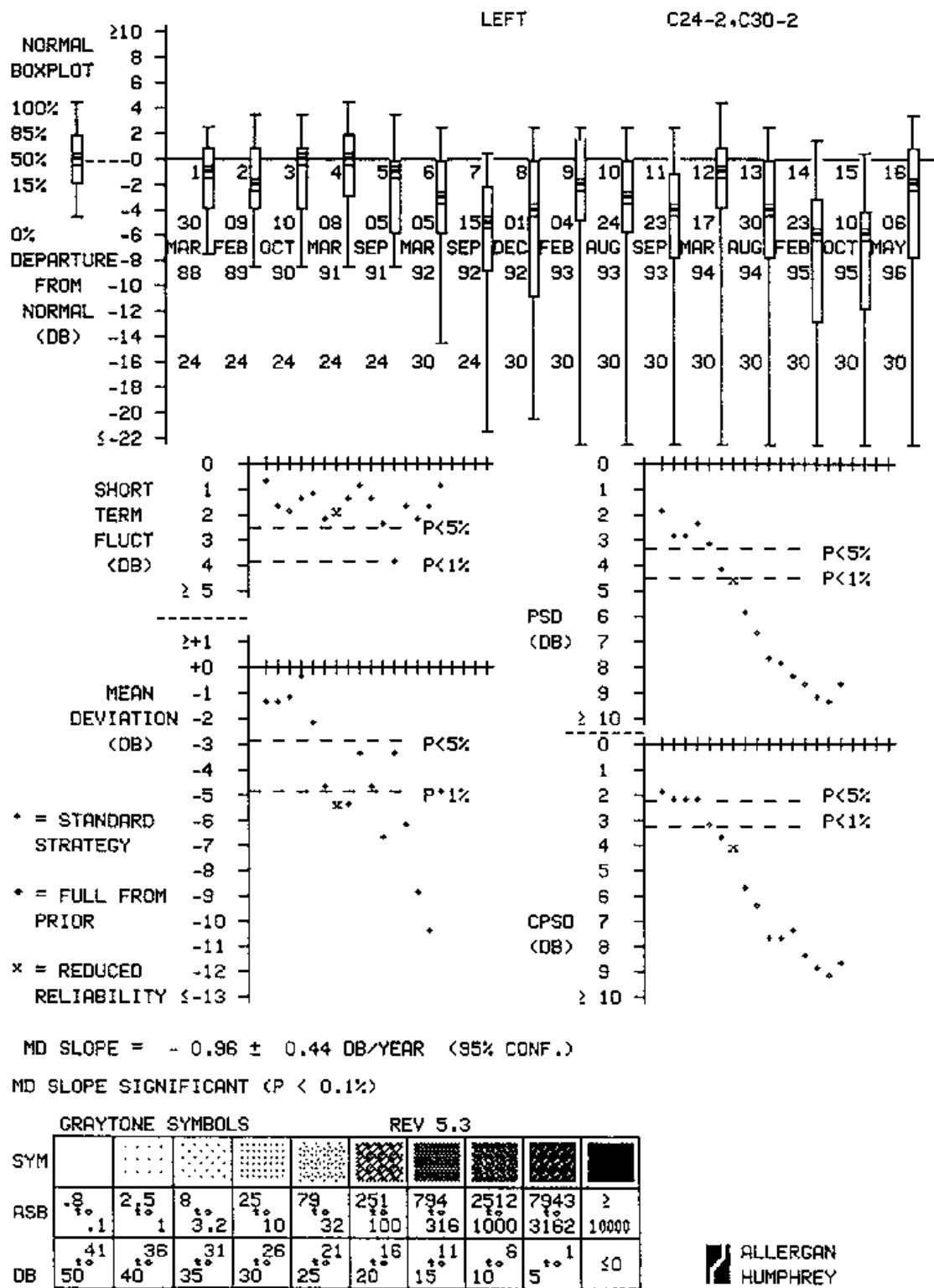


FIGURE 13-13 An example of the change analysis program for the Humphrey Field Analyzer, clearly demonstrating progression of several indices over an 8-year period.

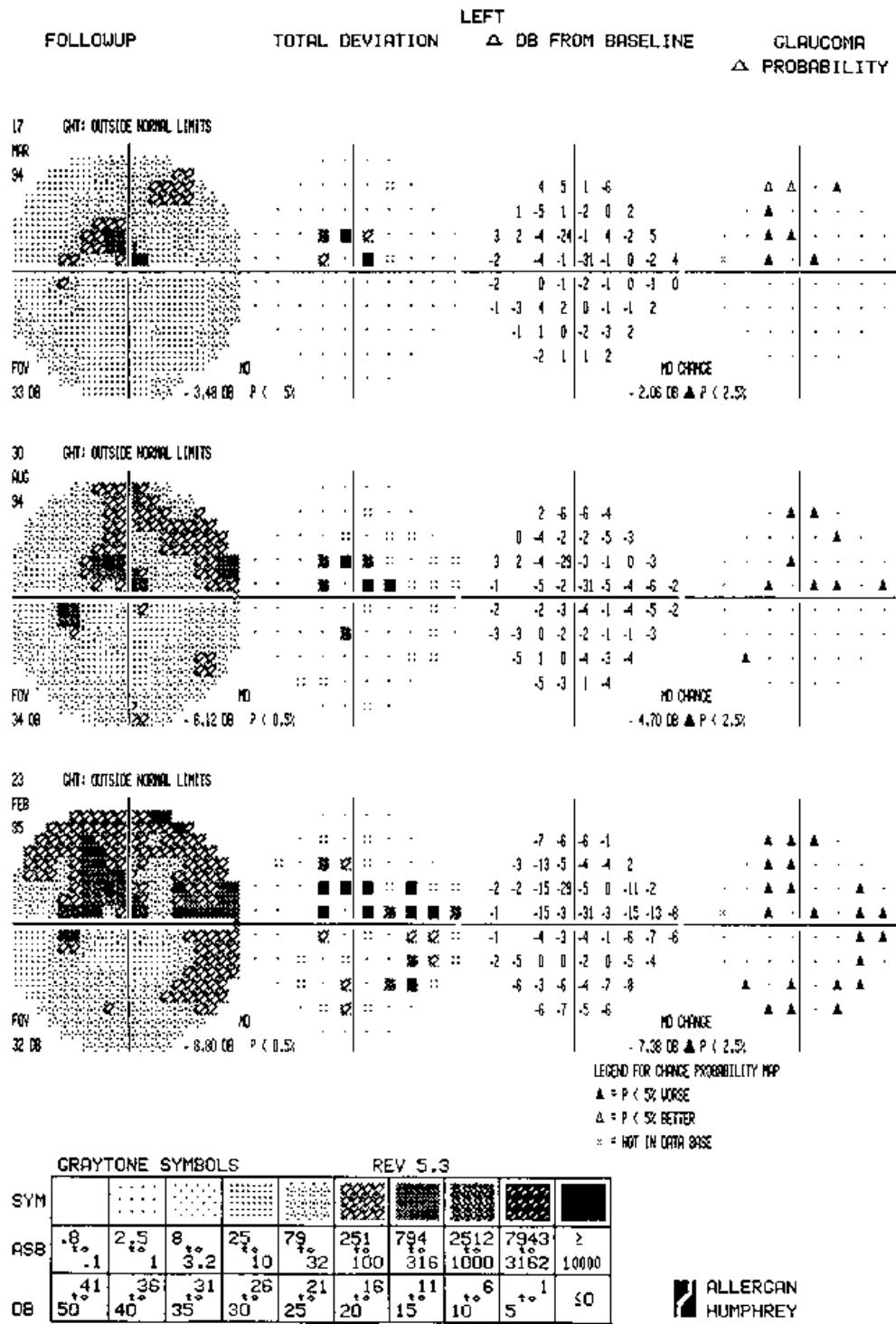


FIGURE 13-14 An example of the glaucoma change probability analysis procedure for the Humphrey Field Analyzer, showing progression from baseline of superior and, later, inferior, arcuate field loss in the left eye of a glaucoma patient.

The “fast” version of this test (SITA-Fast) can reduce test time further, but increased variability makes it less reliable for monitoring glaucoma patients.

Compared with conventional staircase procedures, SITA tests take approximately half as long as the traditional procedures, whereas preliminary findings indicate

SITA has equivalent or slightly lower variability. Although SITA and full threshold tests generally correspond well, SITA results often show less sensitivity loss, and the gray scales generally look better (Fig. 13–15A,B). In spite of this, SITA has lower variability, with smaller probability limits than for conventional automated perimetry, and

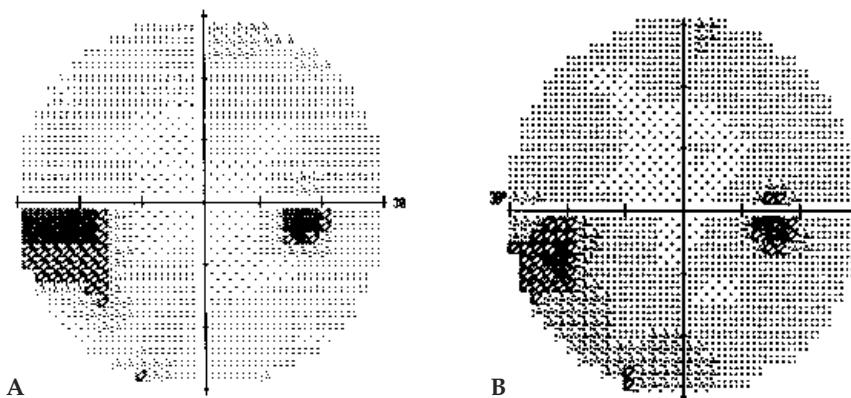


FIGURE 13-15 An example of early glaucomatous visual field loss, as determined by (A) SITA and (B) conventional full threshold test strategies.

requires a smaller amount of sensitivity change to exceed normal limits.

Because of these attributes, along with favorable patient acceptance, the SITA has steadily gained in popularity over the past several years. When switching from full threshold testing to SITA, a new baseline for each patient should be established, similar to that required for converting from manual kinetic to automated static visual field perimetry. Although SITA and full threshold visual field printouts appear quite similar, they are different tests based on distinct principles, and direct comparisons between their results should be made with caution.

PEARL... Patients converting from full threshold automated perimetry to SITA should establish a new baseline, which should always be done when changing from one test program to another.

OTHER TESTS OF VISUAL FUNCTION

Although visual field testing is a valuable tool in the evaluation of glaucoma, it is clear that a substantial number of retinal ganglion cells can be damaged by glaucoma prior to the development of a visual field defect.^{27,28} This indicates that there is still a need for better and more sensitive measures of visual function.

Our understanding of retinal ganglion cell function has expanded rapidly over the past 20 years. We now recognize different types of retinal ganglion cells with distinct anatomical and physiological characteristics.^{29–31} One type of retinal ganglion cells, P-cells, projects to the parvocellular layers of the lateral geniculate nucleus. They tend to have thinner axons and slower conduction velocities and are concentrated in the most central visual field region. Subsets of P-cells are believed to contribute to the processing of color vision information and visual acuity, and perform vision and related functions.

A second major group of retinal ganglion cells, M-cells, projects to the magnocellular layers of the lateral

geniculate nucleus. M-cells generally have thicker axons and faster conduction velocities and are distributed fairly evenly throughout the fundus. Subsets of M-cells are implicated in processing high-frequency flicker, motion information, and other rapid, transient visual stimuli. P-cells outnumber M-cells by about 7 to 10:1.

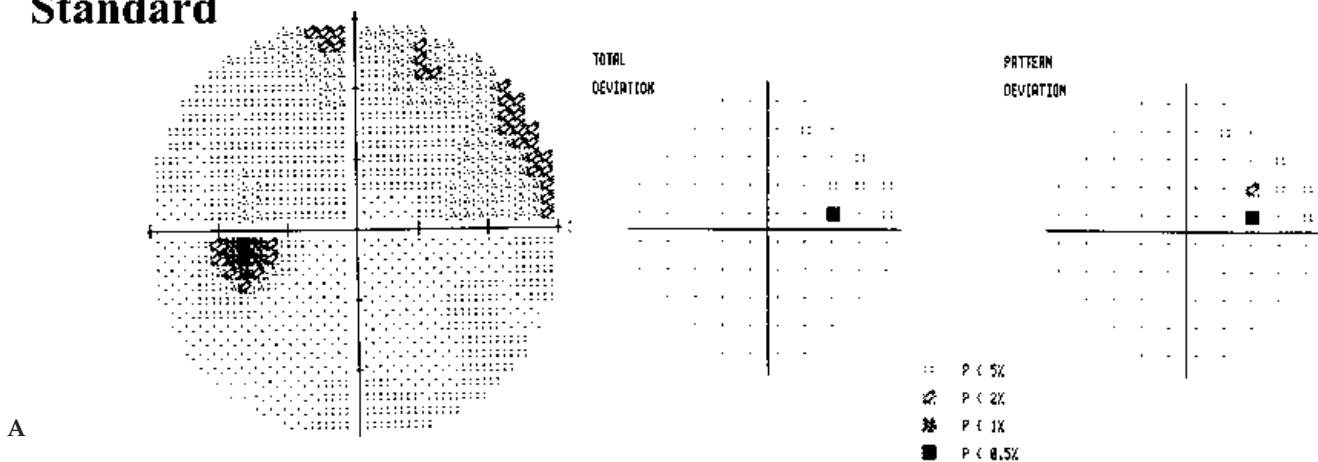
These findings have prompted the development of several new test procedures for evaluating specific subsets of retinal ganglion cells, including the assessment of color vision mechanisms, flicker and motion perception, peripheral visual acuity, and a variety of other visual function tests. As a general rule, tests adapted for perimetric testing of the peripheral visual field are more useful for clinically evaluating glaucomatous functional loss than those that are restricted to testing the fovea or macular region.

SHORT WAVELENGTH AUTOMATED PERIMETRY

Short-wavelength automated perimetry (SWAP), or blue-yellow perimetry, utilizes a bright yellow background (100 cd/m^2) and a large (Goldmann size V) blue stimulus to isolate and assess visual pathways sensitive to short-wavelength light.^{32–41} The bright yellow background helps adapt, or neutralize, the middle (green) and long (red) wavelength-sensitive mechanisms to allow assessment of the short-wavelength color vision mechanisms with the large blue stimulus. All other aspects of SWAP testing are similar to conventional automated perimetry.

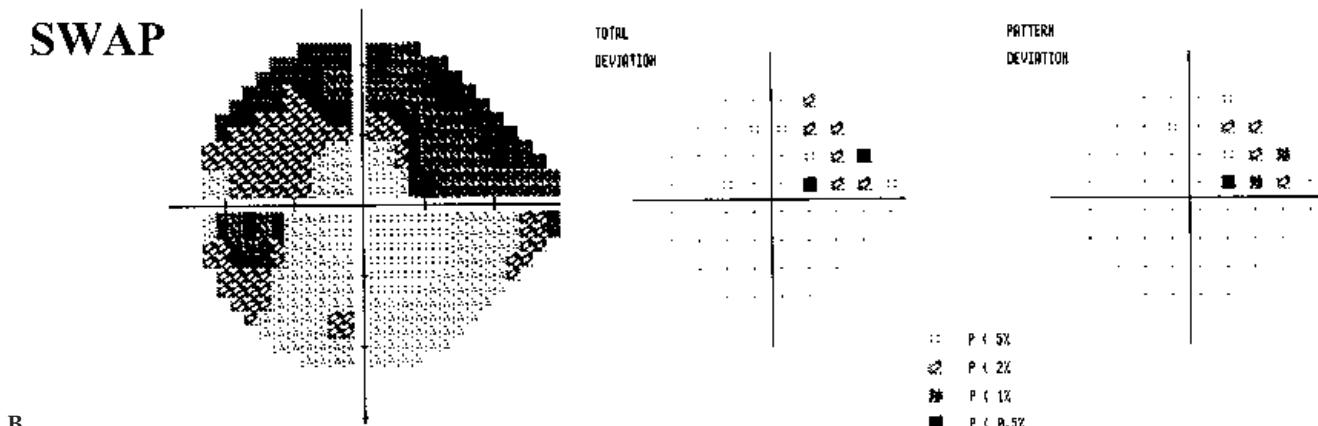
SWAP has undergone a comprehensive validation, with more than 10 years of longitudinal data on hundreds of patients.^{32–40} These findings, in conjunction with reports from other laboratories,⁴¹ have established that (1) SWAP can detect glaucomatous loss approximately 3 to 5 years earlier than conventional automated perimetry, (2) SWAP deficits can predict future visual field defects for conventional automated perimetry, (3) SWAP deficits are more extensive and demonstrate more rapid glaucomatous progression than conventional automated perimetry, and (4) SWAP deficits correlate with early optic nerve head abnormalities in glaucoma, as well as other risk factors associated with the development of glaucoma (Fig. 13–16A,B).

Standard



A

SWAP



B

FIGURE 13-16 (A) A superior visual field defect appears as a subtle nasal step on conventional automated perimetry. (B) Short-wavelength automated perimetry discloses a more extensive arcuate visual field loss.

SWAP is now available as a standard clinical test procedure on the Humphrey Field Analyzer Model 750 and the Octopus 1-2-3, and the former offers a statistical analysis package for SWAP to help interpret the test results.

Two modifications would improve the clinical utility of SWAP. The first is the development of a faster thresholding algorithm, such as the SITA, to shorten the time to 5 minutes per eye. The second would be to increase the dynamic range to make SWAP more useful in patients in whom a cataract has reduced their overall sensitivity.

FREQUENCY DOUBLING TECHNOLOGY PERIMETRY

When a low spatial frequency sinusoidal grating (one cycle per degree or less) undergoes rapid (greater than 15 Hz) counterphase flicker, or alternation of the light and dark bars, there appear to be twice as many bars than are actually present (i.e., the spatial frequency of the grating appears doubled). This phenomenon, possibly mediated by a subset of the M-cell retinal ganglion cells, sometimes referred to as My cells,⁴²⁻⁴³ has been adapted for use as a visual field test.

Contrast sensitivity for detecting the frequency-doubled stimulus is determined at 17 visual field locations

(four 10-degree-diameter targets per quadrant, plus the central 5-degree radius) over the central 20-degree visual field. This test, much faster than conventional automated perimetry, requires about 4 to 5 minutes per eye for full threshold testing and 45 to 70 seconds per eye for the rapid screening test. Both the full threshold and rapid screening procedures have high sensitivity and specificity for detection of glaucomatous visual field loss.⁴²⁻⁴⁸ Frequency doubling technology (FDT) perimetry also demonstrates very good test-retest reliability. It is easy to perform, well received by patients and technicians, and now has an age-adjusted normative database and statistical analysis package (Fig. 13-17A,B). It is currently being evaluated for long-term monitoring of glaucoma patients.

HIGH-PASS RESOLUTION PERIMETRY

High-pass resolution perimetry (HRP) utilizes a high-resolution video monitor to present ring optotypes that consist of a light central region surrounded by a dark one. The targets are high-pass filtered so the stimulus contains only high spatial frequencies. This stimulus is designed to correspond more closely to the center-surround arrangement of

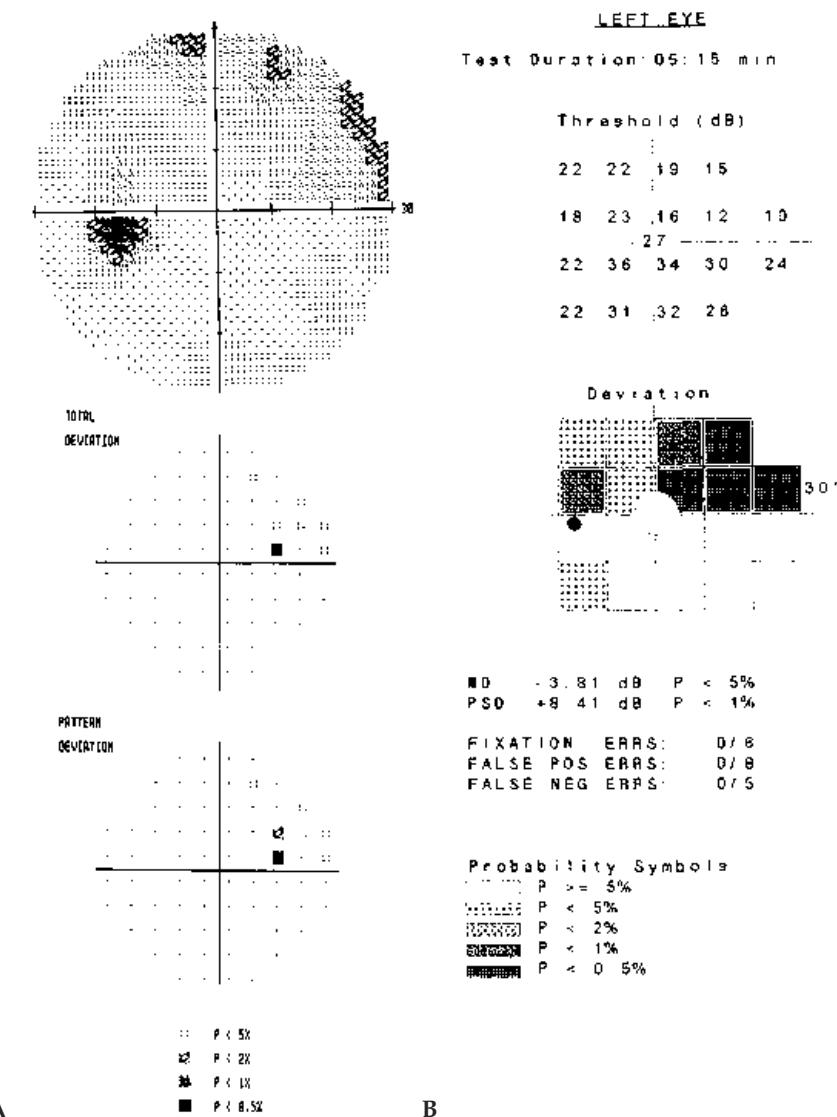


FIGURE 13-17 For the same eye shown in Figure 13-16A,B, the subtle superior nasal step with (A) conventional automated perimetry is compared with (B) a more extensive superior arcuate defect, revealed by frequency doubling technology perimetry.

retinal ganglion cell receptive fields, and therefore might reveal glaucomatous ganglion cell losses more readily than conventional automated perimetry.⁴⁹⁻⁵⁶ Unlike traditional visual acuity optotypes, HRP targets can be resolved at the same size at which they can be detected. By varying target size, HRP determines the minimum size needed to detect the stimulus at various visual field locations.

HRP produces results comparable to conventional automated perimetry for a variety of ocular disorders, including glaucoma.⁴⁹⁻⁵⁶ However, HRP has better test-retest reliability than conventional automated perimetry, especially in patients with significant glaucomatous visual field loss.⁵⁵ Because of this greater reliability, HRP can detect visual field progression in glaucoma approximately 1 to 2 years earlier than conventional automated perimetry.⁵⁶ Patients generally prefer HRP over standard automated perimetry because it is considerably faster, provides feedback to the patient, and is more interactive.

Current disadvantages of the HRP are the lack of standardization in testing equipment from site to site and limited availability of technical support.

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SECTION IV

THE GLAUCOMAS

CLASSIFICATION OF GLAUCOMA

John C. Morrison, M.D.,
and Irvin P. Pollack, M.D.

There are two main classification schemes for glaucoma: (1) that based on the anatomic mechanism of pressure elevation, and (2) that based on the etiology, or underlying ocular or systemic disorder, for the glaucoma. The former primarily separates glaucoma by whether the angle is open or closed, and further subdivides these main categories into primary and secondary forms. Although this allows one to identify the cause of the pressure elevation and can lead the clinician to the appropriate method of controlling the pressure, there are many conditions in which elevated intraocular pressure (IOP) is due to more than one mechanism, depending on the stage of the disease. For example, an eye with uveitic glaucoma may have an open angle that ultimately becomes closed with peripheral anterior synechiae.

As our understanding of the different forms of glaucoma improves, the etiologic classification of the disease based on the underlying ocular or systemic disorder is becoming increasingly useful. When combined with knowledgeable and skillful gonioscopy, this approach allows more effective treatment of the abnormal IOP because the underlying condition itself can be addressed to augment standard antiglaucoma therapy. In addition, identifying the basic cause allows the clinician to recognize conditions that can eventually develop into glaucoma, before producing ocular pathology. This provides the opportunity to apply specific therapy to prevent the patient from developing glaucoma at all. An additional advantage is that this classification can include forms of glaucoma that can be less pressure-dependent, such as normal-tension glaucoma, and improve our ability to treat and protect the optic nerve itself.

BACKGROUND

In 1938, Barkan proposed that glaucoma be classified into two types, based on anatomic characteristics: that with a deep anterior chamber and an open angle, and that with a shallow anterior chamber and a narrow angle.¹ The clinical

value of this distinction, made by gonioscopy, lay in the fact that, whereas the latter was generally responsive to peripheral iridectomy, the former was not, and required a different management. The practicality of this approach ensured its popularity and even allowed the astute clinician to recognize and treat the occludable, narrow angle before the onset of irreversible adhesions and recalcitrant glaucoma.

Over the years, this basic anatomic approach evolved into a classification system based on mechanism, dividing the glaucomas into open-angle, closed-angle, and developmental conditions (Table 14-1). Further subdivisions separated the open-angle glaucomas into pre trabecular forms, usually due to membranous overgrowth; trabecular forms, where the site of aqueous humor outflow obstruction resides in the trabecular meshwork; and post trabecular forms, due to obstruction in Schlemm's canal or, more usually, elevated episcleral venous pressure. Angle-closure mechanisms consisted of anterior conditions, usually resulting from contraction of pre trabecular membranes and peripheral anterior synechiae, and posterior conditions that "push" the iris forward to close the angle, either with or without pupillary block.

TABLE 14-1 ANATOMIC (MECHANISTIC) CLASSIFICATION OF GLAUCOMA

Open-angle glaucomas

Pre trabecular

Trabecular

Post-trabecular

Closed-angle glaucomas

Pupillary block

Nonpupillary block

Developmental glaucomas

The primary advantage of this approach was that it focused the practitioner's attention on the direct cause of aqueous humor outflow obstruction. This can lead directly to the correct therapy or surgical procedure to relieve the elevated IOP.

However, this system also has disadvantages. Because it is primarily limited to those glaucomas where IOP is elevated, it does not include forms of glaucoma with normal IOP. This scheme can also be confusing because there are many glaucoma conditions in which IOP elevation results from more than one mechanism, depending on the stage of the disease process.

CLASSIFICATION OF GLAUCOMA BASED ON ETIOLOGY

We have come to understand that many specific ocular and systemic conditions can produce glaucoma. This has gradually led to a classification of the glaucomas on the basis of etiology, initially described in the 1960s.^{2,3} Shields has since proposed the useful additional concept that all forms of glaucoma begin with "initiating events," followed by structural and functional changes and, ultimately, by optic nerve damage and visual loss.⁴

The system that we have adopted for this text is based on both of these schemes and divides the glaucomas into (1) open-angle glaucomas, (2) angle-closure glaucomas, (3) developmental glaucomas, and (4) glaucomas associated with ocular or systemic conditions. It is a useful, though not perfect, classification.

All glaucomas can be divided into open-angle glaucoma (OAG) or angle-closure glaucoma (ACG) based on the gonioscopic appearance of the angle. The developmental glaucomas and those associated with ocular or systemic conditions can be similarly divided, and could be assigned as subcategories of OAG or ACG. However, it is more convenient and useful to keep these two categories intact because they often present as distinct clinical entities.

Primary open-angle glaucoma accounts for the majority of patients in the OAG category, and this group includes normal-tension glaucoma. The initiating event, or underlying etiology, may reside in the trabecular meshwork, increasing aqueous outflow resistance and IOP. It could also be a genetic predisposition for structural alterations in the optic nerve head that affect the support or nutrition of the optic nerve axons. As we improve our understanding of the genetic basis of these diseases, we will eventually be able to omit the terms *primary* and *secondary* because all forms of glaucoma will have a known etiologic basis, either a genetic or more direct ocular cause.

ACGs independent of other ocular conditions generally develop from primary anatomic conditions that predispose the eye either to pupillary block glaucoma or to gradual shallowing of the anterior chamber angle. Many

of these latter eyes will present with a combination of pupillary block and anatomic angle-closure.

The developmental glaucomas encompass several conditions that all share some form of abnormal development of the anterior chamber angle. They can include congenital glaucoma, as well as those that present in childhood or adolescence. Many are associated with a range of ocular and systemic conditions.

The final category, often designated as the secondary glaucomas, includes a wide variety of interesting and often difficult conditions. These glaucomas typically develop in association with other ocular conditions, many of which are secondary to systemic diseases.

Recognizing these associations serves many useful functions. First, this can lead the clinician to the underlying etiology of the glaucoma, and treating this may provide a useful adjunct to nonspecific pressure-lowering therapy. An example of this is the use of panretinal photocoagulation (PRP) for neovascular glaucoma following a central retinal vein occlusion. PRP significantly diminishes anterior segment neovascularization by reducing the chemical stimulus to the formation of new blood vessels. If applied before the angle becomes completely closed, PRP can reduce neovascularization of the trabecular meshwork and improve the medical control of IOP. Similarly, PRP improves the success of filtration surgery or aqueous shunt implantation, if needed. The etiologic aspect of this system will remain useful and gain increasing importance for into the future as we refine our understanding of the many forms of glaucoma.

This system also helps the clinician recognize the potential of a predisposing condition to develop glaucoma. With this knowledge, early, specific treatment may completely prevent the development of glaucomatous pathology. Again using the example of neovascular glaucoma, the recognition of a central retinal vein occlusion will alert the clinician to look for anterior segment neovascularization and to perform PRP prior to the development of intractable neovascular glaucoma and angle closure, if necessary.

The etiologic classification of glaucoma does not make the anatomic, or mechanistic, classification obsolete. In fact, it is most effective when used in conjunction with careful gonioscopy to separate ACG from OAG and to identify the precise cause of elevated pressure, or early abnormalities that indicate potential trouble. This is even more important given that many of these conditions may have, at various times, an open or closed angle or may pass initially through a stage of OAG and eventually develop a closed angle, evolving into irreversible angle closure.

However, simply identifying the state of the angle, often at a time when the IOP is normal, may fail to recognize the underlying condition and so lose the opportunity to prevent the development of elevated IOP and glaucoma damage. Moreover, many different forms of

TABLE 14-2 CLINICAL (ETIOLOGIC) CLASSIFICATION OF GLAUCOMA

<i>Glaucoma Condition</i>	<i>Open-Angle</i>	<i>Angle-Closure with Pupillary Block</i>	<i>Angle-Closure without Pupillary Block</i>
Primary open-angle glaucoma	x		
Primary angle-closure glaucomas		x	
With pupillary block		x	
Without pupillary block			x
Childhood glaucomas	x	x	x
Glaucomas associated with ocular and systemic disorders (secondary glaucomas)			
Steroid-induced glaucoma	x		
Pigmentary glaucoma	x		
Pseudoexfoliation glaucoma	x		
Neovascular glaucoma	x		x
Iridocorneal endothelial syndromes	x		x
Elevated episcleral venous pressure	x	x	x
Glaucoma from ocular trauma and hemorrhage	x	x	x
Lens-induced glaucoma	x	x	x
Glaucoma from ocular inflammation	x	x	x
Glaucoma from disorders of the retina, choroid, and vitreous	x	x	x
Glaucoma following anterior segment surgery	x	x	x
Glaucoma from intraocular tumors	x	x	x
Systemic diseases and glaucoma	x	x	x

glaucoma can present with a similar angle appearance. For all of these reasons, a combination of historical, systemic, and ocular findings is required to use this system to its best advantage.

In this section of the text, the division of chapters describing the clinical forms of glaucoma primarily follows this etiologic classification, which appears in Table 14-2. Because of the continued importance of assessing the anterior chamber angle, this table also indicates the conditions that can have an open angle, and those that may, in time, produce anatomic closure of the anterior chamber angle, either with or without pupillary block.

Within the scheme illustrated in Table 14-2, we have listed several common conditions that could be considered a subset of a specific etiologic classification. For instance, neovascular glaucoma may be considered a consequence of various retinal disorders. However, because of the clinical importance of these specific forms of glau-

coma, they will be considered on their own and discussed in their own chapters. We believe that this approach will be the most helpful to the physician faced with the task of learning these diseases for the first time, as well as to the busy general practitioner in need of a quick review.

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PRIMARY OPEN-ANGLE GLAUCOMA

Monica Y. Allen, M.D., and Eve J. Higginbotham, M.D.

The open-angle glaucomas constitute the majority of all forms of glaucoma. Patients with primary open-angle glaucoma (POAG) have typical glaucomatous optic nerve damage and characteristic visual field loss. In about 50% of cases, initial measured IOP is above 21 mm Hg. Those patients with elevated pressures but no nerve damage are said to have ocular hypertension, and in some cases, warrant observation. Other patients with characteristic optic nerve damage may not have IOP above 21 mm Hg and are categorized as having normal-tension glaucoma (NTG). To some degree, the differences among these three conditions may reflect a spectrum of optic nerve susceptibility to IOP, although some evidence suggests that POAG and NTG may be distinct entities.

The decision to treat the patient and lower IOP depends on the practitioner's judgment of whether the level of a patient's pressure without such treatment will lead to progressive nerve damage. In many instances, this reflects on the patient's history and clinical findings, as well as the presence of nonocular risk factors, such as age, race, and family history. In general, treatment of IOP relies on medical management, followed by laser trabeculoplasty and, if necessary, glaucoma filtration surgery, implantation of glaucoma drainage devices, and, rarely, diode laser cycloablation.

PRIMARY OPEN-ANGLE GLAUCOMA

OCULAR HYPERTENSION

This diagnosis is generally used to identify patients with IOP above 21 mm Hg, which is two standard deviations above the mean IOP in the population (Chapter 6). In addition, these individuals are distinguished from POAG by the absence of typical glaucomatous optic nerve damage and visual field loss. However, because of the strong association between IOP and glaucoma (Chapter 1), these patients are at increased risk of developing such changes with time, and warrant regular measurement of their IOP and examination for the development of optic nerve dam-

age. Although previous work has reported that the rate of conversion to POAG among ocular hypertensives is approximately 1% per year^{1–3} the recently released Ocular Hypertension Treatment Study (OHTS) suggests that this rate may be almost 2% for this group overall.^{3a} In a subset of patients with IOP greater than 26 mm Hg and corneal thickness less than 555 µm, the rate was just over 7% per year (at 36% after 5 years of follow-up).⁴ Although some authors describe these patients as glaucoma suspects, this term is best reserved for patients with an optic nerve head that looks suspicious for glaucoma, but with normal IOP and no other risk factors for glaucoma.

RISK FACTORS FOR PRIMARY OPEN-ANGLE GLAUCOMA

Chapter 1 provides a thorough description of the epidemiology of open-angle glaucoma. This includes a discussion of several risk factors, the presence of which increase the possibility of a patient having glaucoma (Table 15–1). One of the strongest of these is elevated IOP, and several studies demonstrate that the prevalence of POAG increases progressively with higher levels of IOP.⁵

TABLE 15-1 RISK FACTORS FOR PRIMARY OPEN-ANGLE GLAUCOMA

Intraocular pressure
Optic nerve head cupping
Age
Race
Family history
Thin central cornea
Diabetes mellitus*
Systemic hypertension*
Myopia*
Migraines*

* Controversial

The size of the physiological cup appears to be another possible risk factor for POAG.^{6,7} Eyes with wide, deep physiological cups have been observed to be at higher risk of developing glaucomatous visual field loss. However, as pointed out in Chapter 1, the appearance of glaucomatous cupping and disc asymmetry are not considered risk factors because these characteristics are part of the definition of glaucoma.

Several population-based surveys have also established that the incidence of POAG among adult African Americans is four to five times that of Caucasians.^{8,9} The strong associations of race and family history with POAG suggest that there is a significant genetic basis for many cases of open-angle glaucoma. This also includes the association of steroid response to POAG. All of these considerations are fully discussed in Chapters 1, 2, and 18. Studies also agree that older age is a significant risk factor for POAG.¹⁰ The OHTS confirmed the contribution of age, large horizontal and vertical cup to disc ratio, and higher intraocular pressure.⁴ Two additional risk factors, greater pattern standard deviation on full threshold perimetric testing and thin corneal measurements, were also noted. Additional, less well established risk factors include systemic vascular disease^{11–13} and the presence of diabetes. These are also more fully discussed in Chapter 1.

PEARL... The three most important nonocular risk factors for glaucoma are age, race, and family history. Three important ocular risk factors are elevated IOP, thin corneas and large cups.

PATHOGENESIS

Pathogenesis of Elevated Intraocular Pressure

Elevated IOP usually results from obstruction of aqueous humor outflow. In POAG, this obstruction has been associated with alterations in the conventional outflow path-

ways, the normal structure and function of which are described in Chapter 4. Studies of the pathology of human specimens with open-angle glaucoma have revealed abnormalities in several regions.

Within the trabecular meshwork of glaucomatous specimens, there appears to be a decrease in endothelial cell number,¹⁵ although cellular activity may be increased, with increased basement membrane thickening.^{16–18} Studies also indicate that trabecular meshwork cells are continuously lost throughout adulthood. This phenomenon is particularly striking in patients with POAG and pigmentary glaucoma.^{15,19} Areas in which the denuded trabecular beams are associated with an increase in outflow resistance correspond to a decrease in outflow facility in these conditions. Alterations in endothelial cell function that normally act to maintain normal trabecular function could contribute to increased resistance to aqueous outflow.

Alteration of extracellular matrix components that are produced and maintained by trabecular meshwork cells may also adversely affect the normal aqueous outflow in POAG. Studies reveal several collagen abnormalities within the trabecular meshwork beams in eyes with glaucoma, including fragmentation, altered orientation, and abnormal spacing.^{20–23} Intertrabecular spaces are also decreased.

Another striking alteration in the extracellular matrix of open-angle glaucoma is the appearance of "plaques," which consist of clusters of material within the corneoscleral beams and juxtaganicular meshwork (Fig. 15-1).^{24–25} These plaques appear to be derived from elastic-like fibers that make up a subendothelial tendon sheath. Although the presence of these plaques does increase with age, the total amount of this material is much greater in eyes with open-angle glaucoma.²⁶

However, just the presence of these materials is probably not enough to explain all of the increased resistance to aqueous outflow that occurs in POAG.²⁷ Other abnormalities in open-angle glaucoma specimens include a

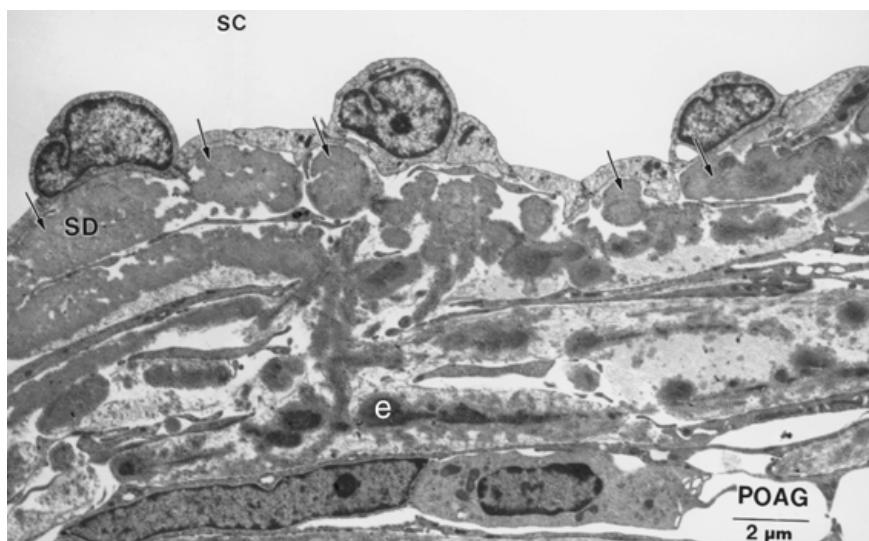


FIGURE 15-1 Transmission electron micrograph of the juxtaganicular meshwork from the eye of a 63-year-old male with POAG. Note the large accumulations of darkly staining tendon and tendon-sheath material (arrows) underlying Schlemm's canal (SC). When cut in cross section, these tendon-sheaths appear as "plaques" of material, also known as sheath-derived plaques (SD). e, elastic tendon (6,250X). (Courtesy of Douglas Johnson, M.D.)

decreased number of giant vacuoles, which are thought to be related to aqueous humor transport (see Chapter 4).^{28,29}

Pathogenesis of Optic Nerve Damage

The pathologic features of glaucomatous optic nerve damage include compression and posterior bowing of the lamina cribrosa, along with loss of optic nerve fibers and abnormal deposition of extracellular matrix materials. These are discussed in Chapter 10, along with potential mechanisms by which elevated IOP can damage optic nerve fibers.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Patients with POAG have few, if any, symptoms in the early stages. In rare cases, a patient with high IOP will note a brow ache, and haloes around lights due to transient corneal epithelial edema. Altered vision usually only occurs in patients with advanced damage, or a scotoma close to fixation. However, in most cases, timely diagnosis depends on careful determination of the history and physical findings.

The pertinent historical points are primarily centered around the ocular and systemic risk factors associated with POAG that were already discussed. Past records, when available, can be particularly helpful in detailing the refractive error, past use of ocular and systemic medications, known local or systemic intolerance to certain medications, and previous ocular surgery.³⁰ An inquiry regarding the severity and outcome of glaucoma in family members and assessment of the impact of visual function on daily living should also be made.

PEARL... When patients report that a family member has glaucoma, the examiner should ask whether the individual had surgery or was just using medication. This may provide some indication of the severity of glaucoma in the family.

When present, altered visual acuity is generally asymmetric and may be worse in the eye with more advanced optic nerve damage. Acquired color vision defects gener-

ally occur in advanced glaucoma, and altered blue-yellow perception is the basis for early detection of visual field loss, as discussed in Chapter 13. A relative afferent pupillary defect may be present in an eye with advanced optic nerve damage in highly asymmetric cases.³¹

Biomicroscopic examination of the anterior segment in POAG is typically normal. However, careful slit-lamp biomicroscopy will help exclude a variety of secondary glaucomas, which may also have open anterior chamber angles. These are discussed in the specific chapters of this section. Specific alterations in the cornea, anterior chamber, iris, and lens can all be useful in detecting or excluding these other diagnoses. Table 15-2 lists several conditions that may closely mimic POAG.

PITFALL... Undiagnosed traumatic glaucoma in a younger patient, or pseudoexfoliation glaucoma in an older patient can mimic asymmetric primary open-angle glaucoma.

As already discussed, the diagnosis of POAG generally includes an IOP measurement > 21 mm Hg. However, several studies have shown that screening pressure measurements of patients with this diagnosis will be less than this nearly 50% of the time.^{5,32} Because of this, and the fact that IOP in glaucoma patients typically fluctuates well beyond that seen in the normal population, measurements taken on several different occasions, and at different times of the day, are often necessary to establish the diagnosis and rule out NTG. Measurement after cycloplegia is also a useful and simple tool for uncovering reduced aqueous outflow facility and a tendency for wide fluctuation in IOP.

Careful evaluation of the optic nerve head is essential for the diagnosis of glaucomatous damage. The techniques for examining the optic nerve head, as well as the features of glaucomatous optic nerve damage are discussed in Chapters 9 and 10. Sommer et al found that decreased visibility of the nerve fiber layer is clinically detectable in 90% of patients with glaucoma at or before the onset of visual field loss.³³ Details, and clinical methods for detecting alterations in the nerve fiber layer, are discussed in Chapter 12.

TABLE 15-2 DIFFERENTIAL DIAGNOSIS OF OPEN-ANGLE GLAUCOMA

<i>Diagnosis</i>	<i>Differentiating Features</i>
Normal-tension glaucoma	IOP < 21 mm Hg on diurnal testing
Ocular hypertension	Lack of optic nerve damage
Pseudoexfoliative glaucoma	Exfoliative material seen on lens capsule with dilation; irregular trabecular pigment
Steroid-induced glaucoma	History of steroid use
Pigmentary glaucoma	Iris transillumination defects, concave iris contour, marked trabecular pigment
Undiagnosed traumatic glaucoma	Subtle angle recession; pigment deposition in angle; history of trauma
Juvenile onset glaucoma	Anterior iris insertion
Mild inflammatory glaucoma	Subtle anterior chamber cells and flare
Elevated episcleral venous pressure	Dilated episcleral veins

Optic disc imaging techniques are discussed in Chapter 11. Because the goal of POAG diagnosis and treatment is to prevent functional vision loss, visual field testing is essential for both the initial evaluation and long-term monitoring of glaucoma patients. Chapter 13 presents details of both manual kinetic and automated static perimetry, and their application to glaucoma management.

NORMAL-TENSION GLAUCOMA

BACKGROUND

NTG has been a diagnostic, therapeutic, and categorical dilemma since its original description by von Graefe in 1857.³⁴ Most authors agree that NTG is characterized by typical glaucomatous optic neuropathy with characteristic field defects. However, the concept of NTG challenges us to distinguish between pressure-dependent and pressure-independent causal factors.

Kamal and Hitchings attempted to simplify the definition of NTG with the following criteria:³⁵

1. A mean IOP without treatment less than or equal to 21 mm Hg on diurnal testing, with no measurement greater than 24 mm Hg
2. Gonioscopically open anterior chamber angles
3. Absence of any secondary cause for a glaucomatous optic neuropathy (i.e., trauma, topical steroid use, or uveitis)
4. Typical optic disc damage with glaucomatous cupping and loss of neuroretinal rim
5. Visual field defect compatible with the glaucomatous cupping
6. Progression of glaucomatous damage

Because of practical and ethical considerations, it may not be possible to wait for clear progression before making this diagnosis.

Based on this definition, up to one third of cases diagnosed as POAG can be classified as having NTG.³⁶ Although NTG is primarily a disease of the elderly, a significant number of patients less than 50 years of age also carry the diagnosis.³⁷ Some studies also suggest that NTG is more prevalent among women, among whom the disease may have a worse prognosis.³⁵

PATHOGENESIS

Some cases of NTG may not be distinct from POAG, but rather result from heightened sensitivity to otherwise normal IOP. IOP in NTG tends to be higher than in the normal population.³⁷ In addition, in NTG patients with asymmetric IOP, the eye with the higher pressure generally has worse optic nerve damage.^{38,39} This is supported by the Collaborative Normal-Tension Glaucoma Study, which is discussed in the following text. Along these same lines, Burgoyne, studying the optic nerve head as a biomechanical structure, has demonstrated that anatomic

features of the optic nerve head may increase its susceptibility to a wide range of otherwise normal IOPs.⁴⁰ Thus, some specific mechanisms of optic nerve damage in NTG may be similar to those postulated for POAG, which are considered in detail in Chapters 10 and 38.

In the absence of clearly elevated IOP, other investigators have looked for other pressure-independent causes to account for the progressive optic nerve damage seen in this condition. Foremost among these factors are various conditions that may alter blood flow to the optic nerve head. Drance et al have described a nonprogressive form of NTG, usually associated with shock or an episode of severe blood loss.⁴¹ Progressive NTG has been associated with vasospasm, systemic hypotension, and abnormal blood coagulability.

Corbett et al first described an increased incidence of migraines among patients with NTG relative to patients with POAG.⁴² Drance et al also showed that digital blood flow to capillaries in the finger was decreased, with and without exposure to cold, in patients with NTG as compared with controls.⁴³ In addition, color Doppler imaging techniques have demonstrated that some NTG patients have increased ophthalmic and central retinal artery resistance.⁴⁴

The role of systemic hypotension in NTG has also been investigated. Hayreh et al found a greater nocturnal decrease and a lower level of diastolic blood pressure in NTG relative to patients with anterior ischemic optic neuropathy and POAG.⁴⁵ Finally, studies have found no conclusive evidence that NTG patients overall have an abnormal coagulability profile, although this possibility should be considered with each individual patient.⁴⁶

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of NTG is similar to that of POAG. NTG is also an insidious disease and often lacks symptoms until central vision is threatened. Important historical details include a history of shock or severe blood loss, migraines, and cold hands (Raynaud's phenomenon).

The ocular examination is essentially the same as with POAG, with some key distinctions with regard to the optic nerve head and the visual field. Although the optic atrophy of NTG appears similar to that of POAG, Miller and Quigley noted a structural difference in the cribriform plate between the two conditions, and speculated that microscopic differences may contribute to an increased susceptibility to pressure damage.⁴⁷ Studies also suggest that NTG patients have more advanced neuroretinal rim loss and peripapillary atrophy, as well as a higher incidence of optic disc hemorrhages.^{48,49} Others have reported that the visual field defects in NTG are closer to fixation, have a steeper slope, and are of greater depth than with POAG.⁵⁰ Some authors feel that these differences support the notion that these are distinct clinical entities. However, other studies do not support these findings.⁵¹

The most important entity in the differential diagnosis of NTG is undetected POAG. Because a compromised outflow

facility can produce marked variation in diurnal IOP, intermittent IOP elevations could go unnoticed, leading to a clinical picture consistent with NTG. Systemic medications can also mask elevated IOPs.⁵² Diurnal IOP measurements, or measurements taken at several different times over a period of days, are essential to rule out this possibility.

Pigmentary glaucoma that has spontaneously remitted, due to decreased pigment load in the trabeculum with age and improved outflow facility, has also been documented as an apparent cause of a nonprogressive NTG.⁵³ A similar picture can result from elevated IOP due to past use of topical or systemic corticosteroids, where glaucomatous optic nerve damage remains after cessation of the offending medication and return of the IOP to normal. Secondary glaucomas that can lead to episodic elevations of IOP, such as uveitic glaucoma, can be occasionally confused with NTG. All of these entities are discussed in their respective chapters later in this section.

Several nonglaucomatous neurological and vascular entities can mimic the glaucomatous optic neuropathy of NTG.⁵⁴ Neurological causes include congenital anomalies, such as an optic nerve pit, optic nerve coloboma, and morning glory syndrome. Compressive lesions of the optic nerve, due to an intracranial aneurysm or tumor, should also be considered. However, patients referred for evaluation of NTG by computed tomography or magnetic resonance imaging generally show no greater incidence of intracranial disease than in the general population, outside of small vessel ischemic changes.³⁵ Neuroimaging of suspected NTG patients is probably best performed when pallor of the neural rim appears excessive, compared with the degree of cupping.

Vascular diseases, such as prior episodes of shock or anemia,⁵⁵ and anterior ischemic optic neuropathy⁵⁶ (Chapter 10 Fig. 10–5) can also produce optic atrophy similar to that of glaucoma. In general, it is best to refer patients to a neurologist or neuro-ophthalmologist for further assessment if they do not demonstrate typical glaucomatous correlation between the disc and field, or if they complain of symptoms that cannot be explained by their visual loss.

MANAGEMENT OF OPEN-ANGLE GLAUCOMA

OCULAR HYPERTENSION

As indicated above, management of ocular hypertension generally consists of periodic monitoring of the IOP and of the status of the optic nerve and visual field. Treatment is generally begun if the patient develops optic nerve or visual field damage, or if the IOP climbs above a specified level, usually around 30 mm Hg. Several studies have produced conflicting conclusions on the value of prophylactic treatment of IOP.^{57,58} However, after 60 months of follow-up, the OHTS clearly showed that reducing IOP by 20% with glaucoma medications decreased the risk of developing glaucomatous visual field loss from 9.5% in the untreated control group to 4.4% in the treatment group.^{3a} An impor-

tant companion paper identified certain factors that were associated with a higher risk of progression and may lead a clinician to suggest therapy.⁴ These factors included age, large vertical or horizontal cup to disk ratio, an abnormal pattern standard deviation on VF analysis, and a corneal thickness less than 555 µm. However, the decision to treat an ocular hypertensive should be based on not only an individual's array of risk factors but on other factors as well, such as systemic health and life expectancy.

PRIMARY OPEN-ANGLE GLAUCOMA

Choosing a Target Pressure

IOP is presently the only variable in POAG that can be treated. Therefore, the decision to treat a patient depends on the practitioner's judgment of whether the patient's IOP without treatment will lead to progressive nerve damage. This also involves determining a stable range of pressures unlikely to cause further optic nerve damage. The upper limit of this range is defined as the target pressure or pressure goal. This target pressure varies among patients and may need to be modified during the course of the disease if field loss continues despite IOPs within the target range.

Table 15–3 highlights various controlled clinical trials of glaucoma therapy.^{59–68} These studies of several types and stages of POAG have helped to clarify the value of reducing IOP to inhibit progression of the disease. These studies also give better insight into which therapeutic options may be best suited for patients of particular ethnic backgrounds. For instance, in the Advanced Glaucoma Intervention Study (AGIS), the group of patients with the most stable visual fields had IOPs less than 18 mm Hg and had an average IOP during the follow-up of 12 mm Hg or less.⁶⁶

Although it is difficult to specify exact guidelines for target IOP levels, the following levels may be used as a reasonable guide.⁶⁹

1. Any IOP greater than 32 mm Hg should be reduced to at least the low 20s.
2. Eyes with cup-to-disc ratios greater than 0.5, slight asymmetry of the cup-to-disc ratio or IOP, high myopia, a strong family history of glaucoma, or African ancestry should have IOPs lowered below 21 mm Hg.
3. Patients with early glaucomatous optic disc damage and visual field loss above or below central fixation should have IOPs below 18 mm Hg.
4. Patients with moderate to advanced glaucomatous optic disc damage (cup-to-disc ratios greater than 0.8) and superior and inferior arcuate scotomatous visual field loss should have IOPs consistently below 15 mm Hg (many practitioners would choose a target of 12 mm Hg).
5. Patients with advanced glaucomatous optic disc damage (cup-to-disc ratios greater than 0.9) and extensive visual field loss within the central 10 degrees of fixation require an IOP below 12 mm Hg.

TABLE 15-3 CLINICAL TRIALS

Name	Study Design	No. of Patients	Follow-up Duration	Results
Ocular Hypertension Treatment Study ^{3a,4,59}	IOP > 21 mm Hg, no disc or VF damage: effect of 20% medical lowering of IOP vs observation on visual field loss/nerve damage	1,637 (25% black)	5+	20% lowering of IOP reduced risk of developing glaucomatous VF loss from 9.5% to 4.4%. Age, disc damage, IOP, and corneal thickness associated with conversion to POAG.
Scottish Glaucoma Trial ⁶⁰	Newly diagnosed POAG: medicine vs trabeculectomy	99	3–5 years	Trabeculectomy lowered IOP more than medicine; those treated with medicine lost more visual function than those with trabeculectomy.
Moorfields Primary ⁶¹ Treatment Trial	Newly diagnosed POAG: medicine vs laser trabeculoplasty vs trabeculectomy	168	5+ years	Trabeculectomy lowered IOP more than medicine or laser; trabeculectomy group also maintained more visual function than medicine or laser group.
Early Manifest Glaucoma Trial (EMGT) ⁶²	Newly diagnosed POAG: treatment with ALT plus beta blocker vs no treatment	255	4+ years	Ongoing study
Collaborative Initial Glaucoma Treatment Study (CIGTS) ^{63,63a}	Newly diagnosed POAG: immediate filtering surgery vs initial treatment with medication	607 (38% black)	5+ years	No difference in VF change between treatment modalities. Higher rate of cataracts with filtering surgery.
Glaucoma Laser Trial (GLT) ⁶⁴	Newly diagnosed POAG	203	6–9 years	Initial laser trabeculoplasty found as effective as initial topical timolol to lower IOP and preserve vision.
Advanced Glaucoma Intervention Study (AGIS) ^{65,66}	Black and white patients with advanced POAG: laser trabeculoplasty first vs trabeculectomy first, followed by opposite intervention if first intervention fails	581 (57% black)	7 years	Greater IOP reduction with trabeculectomy first. For black patients, better visual preservation with laser first; for white patients, better visual preservation with trabeculectomy first. ⁶⁵ Low IOP associated with reduced visual field defect progression. ⁶⁶
Normal-Tension Glaucoma Study ^{67,68}	Combination of medical, laser, and surgical treatment to produce a 30% reduction in IOP vs no treatment in patients with progressing normal-tension glaucoma	140	5 years	Reduction of normal pressures by 30% slowed the rate of glaucomatous progression in a significant number of patients.

IOP, intraocular pressure; POAG, primary open-angle glaucoma; ALT, argon laser trabeculoplasty; VF, visual field.

In general, the patient's IOP and optic nerve should be monitored every 3 to 4 months, with yearly visual fields. More frequent examinations are needed in patients with advanced optic nerve damage or following a change in treatment.

Medical Management

The physician should always remember that the decision to start a patient on glaucoma treatment frequently commits the patient to a lifetime of topical or systemic med-

ication. Gutierrez et al have shown that health-related quality of life among patients diagnosed with glaucoma differs from normal controls. This difference is likely due to the medications because it appears to be independent of visual acuity or visual field considerations.⁷⁰

Before starting medical therapy, the disease process, the rationale and goals of treatment, and the relative benefits and complications of alternative interventions should be explained to the patient. This allows the patient to understand the need for treatment and help develop a

treatment plan, all of which will help maximize compliance. The clinician should also instruct the patient in proper techniques for taking and using medications, including eyelid closure and punctal occlusion, to minimize side effects and complications, as outlined in Chapter 31.

The overriding goal of medical treatment for glaucoma is to use the least number of medications necessary to achieve the target IOP, with the minimum ocular and systemic side effects. Usually one medication is changed (either added or subtracted) at a time and the IOP is measured before another change is made. If the medication does not lower IOP by 15 to 30% compared with baseline, or if it proves intolerable, it should be discontinued and a different one tried.

Beta-blockers are commonly selected for initial medical management. This is because they have relatively few ocular side effects and can be used once or twice a day, and we have decades of experience with their use for glaucoma. The disadvantages of beta-blockers, their pharmacology, and the different formulations are all discussed in detail in Chapter 33. Latanoprost, the first available prostaglandin analog, has recently been joined by three other agents (Chapter 35). All are systemically well tolerated and are gaining popularity as first-line drugs, depending on patient age and other individual variables.

Adrenergic agonists, topical carbonic anhydrase inhibitors are generally considered second-line drugs in the management of POAG. These classes of medications, their efficacy, and their relative advantages and disadvantages are all discussed in Chapters 32 and 36, respectively.

These different classes of drugs may all be added to beta-blockers and to one another to help further lower IOP. However, using two or more medications from the same category rarely provides an additional benefit. Multiple eye drops should be separated by 5 minutes to allow complete absorption before the next drop is given. Another option may be to use combination drops to improve patient compliance and take advantage of additive effects. The combination of timolol maleate and dorzolamide hydrochloride is now available, and the synergistic effect of a combination drug consisting of timolol and latanoprost is currently under investigation.

Systemic carbonic anhydrase inhibitors may be added if the IOP is uncontrolled on maximal tolerated topical medical therapy or in situations when the IOP is extremely elevated. The patient's tolerance may dictate whether these medications are used for the short or long term. Advantages and disadvantages of these medications are discussed in Chapter 36.

If the IOP begins to rise after long-term treatment with a particular medical regimen, there may be loss of responsiveness to the medication (drift) or continued progression of the disease. The clinician may here consider a trial of a different medication rather than adding a medication to the medical regimen. One study found that when treatment was switched from timolol to latanoprost, IOP was reduced by an additional 1.5 ± 0.3 mm Hg.⁷¹

CONTROVERSY

Switching to another drug versus adding a second drug will be dependent upon the initial pressure reduction and the comparative efficacy of the first and second drug when used separately.

Parasympathomimetic (miotic) agents, most commonly pilocarpine, have now been relegated to a third-line medical therapy. Although they have few systemic complications and are relatively inexpensive, and their popularity is limited by multiple ocular and visual side effects (Chapter 34).

Neuroprotection, or the use of medications designed to protect the optic nerve directly, has gained increased attention in recent years. Although no neuroprotective agent has yet been proven effective in glaucoma, several possibilities and concepts are discussed in Chapter 38.

Laser Management

Most patients with POAG can be controlled by antiglaucoma medications. Alternatively, argon laser trabeculoplasty (ALT) provides a clinically significant reduction of IOP in approximately 75% of initial treatments.⁷² The advantages of trabeculoplasty over medical treatment include lack of systemic adverse effects, minimal required patient compliance, and decreased incidence of ocular problems that could possibly compromise subsequent surgical therapy.⁷³

Because it lacks the complications of filtering surgery, trabeculoplasty should also be considered for patients inadequately controlled on maximum medical therapy. However, it seldom reduces the number of required glaucoma medications. The AGIS noted that, in African American patients uncontrolled by medical therapy, initial treatment with ALT provided better preservation of visual function than trabeculectomy (Table 15–3). The indications and technique of this treatment are discussed fully in Chapter 40.

Surgical Management

Filtering surgery is indicated in patients who have shown progressive visual field loss or optic nerve damage on maximum tolerated medical therapy and after appropriate laser treatment. Specific indications for primary filtering surgery include the following:⁷⁴

1. Patients who are poor candidates for conventional medical management
2. Patients in whom a target IOP level is unlikely to be achieved with topical medications
3. Visual field loss such that any further progression would affect the patient's quality of life

4. Patients who have a known rate of progression such that quality of life would suffer unless rapid IOP stabilization occurs at a target pressure level

Filtering surgery reduces IOP and often eliminates the need for medical treatment. Although effective in 85 to 95% of previously unoperated eyes, the potential success of the operation must be measured against the potential effect of complications on the patient's quality of life.

Although long-term control is often achieved with filtering surgery, many patients will require repeat surgery or supplemental medical management, or both. Specific filtering surgery techniques, the adjunctive use of antimetabolites, and potential complications are discussed fully in Chapter 43. Glaucoma surgery in patients with cataracts is considered in Chapter 44, as well as glaucoma surgery combined with cataract extraction, which may be indicated in patients who require visual rehabilitation with cataract extraction, in addition to IOP lowering.

Aqueous drainage devices are generally reserved as a last resort for patients with glaucoma that is refractory to standard filtering surgery (Chapter 45). This includes patients with extensive conjunctival scarring, chronic inflammation, and ocular trauma. IOP lowering with glaucoma drainage devices is generally not as effective as with filtering surgery.

Finally, cyclophotocoagulation is another alternative for patients with glaucoma that is refractory to other interventions. The indications, advantages, and disadvantages are discussed in Chapter 42.

NORMAL-TENSION GLAUCOMA

Current treatment of NTG also consists of lowering IOP enough to protect the optic nerve from progressive damage. Some believe that progression of disease should be documented prior to initiation of therapy because of this pressure-dependent goal, although this is not practical in patients with advanced visual field loss.⁵² The Normal-Tension Glaucoma Study found that a 30% reduction in IOP reduced the risk of progression, although a substantial minority of these patients still suffered visual field deterioration.^{67,68} In other patients, a pressure reduction less than 30% may be adequate. Close observation and assessment of the patient's risk factors and pertinent ocular history should aid the clinician in determining the appropriate goal for the IOP. As with POAG, complications from medical and surgical therapy should be weighed against the benefit of treatment prior to initiating each therapy.

As with glaucoma from any cause, initial therapy of NTG is usually medical. In addition to conventional topical medical management, systemic calcium channel blockers have also been recommended because they may reverse the vasoconstriction thought to be involved in the pathogenesis of the disease. Netland et al. found that NTG patients who were on calcium channel blockers for medical reasons were less likely to progress.⁷⁵ Currently,

these drugs are not widely used for NTG, due to systemic side effects usually orthostatic hypotension, and the difficulty in demonstrating a clear benefit.

Some work suggests that topical betaxolol may also improve ocular blood flow in NTG.³⁵ However, glaucoma patients on aggressive antihypertensive regimens, including beta-blockers and calcium channel blockers, may have a larger nocturnal decrease in systolic pressure, reduced ocular perfusion pressure, and a greater tendency for deteriorating visual fields.⁴⁵

Medical treatment of NTG is followed by progression to laser and surgical management, as dictated by the status of the optic nerve and visual field. Trabeculectomy with antimetabolites is the treatment most likely to achieve substantial IOP lowering. However, this also carries the risk of postoperative hypotony,⁷⁶ and filtering surgery is probably best reserved for those patients with significant visual field loss or progression.

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ANGLE-CLOSURE GLAUCOMA

Irvin P. Pollack, M.D., and Jacob Wilensky, M.D.

Glaucoma associated with a closed anterior chamber angle can occur either by temporary apposition of the peripheral iris to the trabecular meshwork (appositional closure) or by permanent adhesions in the anterior chamber angle (peripheral anterior synechiae). The former situation results from relative obstruction of the movement of aqueous humor into the anterior chamber, termed pupillary block. This can occur as a primary condition, without associated ocular abnormalities, and present as either an acute, intermittent, or chronic glaucoma (Table 16-1). Careful gonioscopy generally allows the practitioner to identify this condition and perform laser iridotomy to permit aqueous humor to bypass the pupil and relieve the pupillary block. A patent iridotomy will generally deepen the anterior chamber angle in these situations, unless the patient also has a nonpupillary block form of angle closure or intermittent or chronic angle closure that has resulted in permanent adhesions.

Secondary forms of pupillary block glaucoma generally result from a variety of inflammatory and other ocular conditions that produce posterior adhesions between the lens and pupillary border (posterior synechiae). These are best managed by peripheral iridotomy in combination with specific treatment of the underlying condition.

Nonpupillary block angle closure may occasionally present as a primary condition, termed plateau iris configuration, which appears to result from forward displacement of the ciliary processes. Glaucoma with plateau iris configuration occurs when the peripheral iris becomes apposed to the trabecular meshwork. Diagnosis requires the presence of a patent iridotomy to rule out the possibility of pupillary block.

The most common forms of nonpupillary block angle-closure glaucoma typically occur secondary to intraocular surgery or other precipitating conditions. Here, the peripheral iris is forced into apposition with the trabecular meshwork and peripheral cornea. This can occur either by “pulling” mechanisms, such as peripheral anterior synechiae due to intraocular inflammation and neovascularization of the angle, or diseases of the surrounding tissues, such as the iridocorneal endothelial (ICE) syndrome, aniridia, and iridoschisis. In other cases, the peripheral iris is “pushed” into the angle by conditions such as suprachoroidal hemorrhage and uveal tumors, or swelling or anterior rotation of the ciliary body, usually due to several posterior segment diseases and surgical procedures. Treatment of the underlying condition is always required to manage these forms of angle-closure glaucoma, along with standard medical and surgical glaucoma treatment.

TABLE 16-1 ANGLE-CLOSURE GLAUCOMAS

Primary angle closure with pupillary block
Acute
Intermittent
Chronic
Combined mechanism
Secondary angle closure with pupillary block
Primary angle closure without pupillary block (plateau iris syndrome)
Secondary angle closure without pupillary block

PRIMARY ANGLE CLOSURE WITH PUPILLARY BLOCK

BACKGROUND

History

Until the mid-19th century, acute glaucoma was a painful eye disease usually treated by purging, bloodletting, and leeching.¹ In 1856, Albrecht von Graefe performed an iridectomy on a 51-year-old woman with acute glaucoma

and found that it produced a lasting beneficial effect. He announced his discovery at the First International Congress in Brussels in 1857, after which a large sector iridectomy that involved tearing the iris away from its root became the standard procedure for this disease.² It was later recognized that a smaller iridectomy located in the peripheral iris was also effective.³

By the early twentieth century, the ultimate failure of many iridectomies led surgeons to develop the filtering operation combined with iridectomy as the procedure of choice for chronic glaucoma. However, the mechanism by which iridectomy relieved the high pressures in some cases of glaucoma was uncertain. Three main theories prevailed: it removed enough iris to relieve the block of aqueous by iris in the angle; it caused a subconjunctival filtering scar; and aqueous was absorbed through the cut edges of the iris.⁴

At this time, Curran noticed that in some cases the eye pressure was controlled after a filtering operation even though the bleb had failed. Dr. Curran observed that the iris lay closely against the lens, and that aqueous bypassed the pupillary block by flowing through the iridectomy. In 1920, he developed his theory that some forms of chronic primary glaucoma were caused by a relative pupillary-block mechanism, resulting in angle-closure glaucoma.⁵ This monumental work led to the use of the peripheral iridectomy as a specific treatment for pupillary-block glaucoma, established the etiology of this condition, and saved many eyes that would have been lost had they been treated by the relatively crude, previously used filtering procedure. During the next several years Banziger,⁶ Raeder,⁷ and Rosengren⁸ independently proposed similar theories concerning the mechanism of pupillary block in eyes with shallow anterior chambers.

In 1900, Trantas devised a method of direct ophthalmoscopy to examine the anterior chamber angle. He described the ophthalmoscopic appearance of the normal and abnormal angle and was the first to use the term *gonioscopy*.⁹ Salzmann used a modified contact lens to see the angle and described peripheral anterior synechiae (PAS), angle recession, and other abnormalities.¹⁰ Troncoso¹¹ designed a hand-held microscope that required a light source and, when used with the Koeppe lens,¹² provided an excellent direct view of the angle. In 1936, Barkan showed that people who developed attacks of angle closure had gonioscopically closed anterior chamber angles and that the angle of the fellow eye was narrow.

The work of these investigators confirmed the mechanism of angle-closure glaucoma, and, in 1938, Barkan classified glaucoma into open-angle and angle-closure forms.¹³ This classification was further defined by Sugar and ultimately was adopted by leading ophthalmologists.¹⁴ Thereafter, gonioscopy was recognized as an important diagnostic tool, and it became widely accepted that peripheral iridectomy was the procedure of choice in preventing closed-angle attacks in eyes that were predisposed to pupillary block.

Epidemiology (see also Chapter 1)

The number of people with primary glaucoma has been estimated at nearly 66.8 million, with 6.7 million suffering from bilateral blindness. It is the second leading cause of vision loss in the world.¹⁵ In many countries, angle closure is the commonest form of primary glaucoma and is responsible for a large percentage of this glaucoma-blind population.

In most Western countries, the ratio of primary open-angle glaucoma (POAG) to primary angle-closure glaucoma (PACG) is 5:1.¹⁶ However, there is a sharp reversal of this trend among the Inuit of Alaska and Greenland, where the overall prevalence of PACG is 0.44%, compared to 0.01% for POAG.^{17,18} In this population, angle-closure glaucoma makes up 80 to 90% of primary glaucoma, with a prevalence of 2 to 8%.¹⁹

Nearly half of the world's blind population resides in East Asia,²⁰ and the majority of these have angle-closure glaucoma. This includes Chinese, Burmese, Malays, Filipinos, and Vietnamese.^{19,21,22} In Mongolia, PACG accounts for three out of every four cases of glaucoma, and some 6.4% of the population is judged to have gonioscopically occludable angles.^{23,24}

SPECIAL CONSIDERATION

Nearly half of the world's blind population resides in East Asia. The majority of these have angle-closure glaucoma.

Primary acute angle-closure glaucoma with pupillary block occurs less frequently among Africans,²⁵ African Americans,²⁶ and South Africans²⁷ where the disease usually manifests itself as chronic angle-closure glaucoma.²⁸⁻³¹ Pupillary-block glaucoma also occurs infrequently in the South Pacific and among American Indians.

The prevalence of PACG with pupillary block increases with age,^{32,33} and most cases of acute angle closure occur in the sixth and seventh decades of life.³⁴ However, angle-closure glaucoma can occur at any age, including young children.³⁵ Women are afflicted with angle-closure glaucoma two to four times as often as men.³⁶⁻³⁹ In Singapore, elderly women were in the highest-risk group for developing acute PACG.⁴⁰

PATHOPHYSIOLOGY

The most common form of PACG occurs in shallow-chambered eyes where the aqueous humor cannot pass freely from the posterior chamber, through the pupil, and into the anterior chamber. This is caused by apposition of the iris pupil against the underlying crystalline lens. When the resistance produced by this iridolenticular block surpasses the pressure in the posterior chamber (relative pupillary block), then the peripheral iris will be pushed



FIGURE 16-1 Pupillary-block glaucoma results from blockage of aqueous humor behind the pupil. The pressure builds up in the posterior chamber and pushes the peripheral iris forward to cause iris bombé and angle closure.

forward (iris bombé) and occlude the angle if it is narrow to begin with (Fig. 16-1). If the angle approach is wide, then any buildup of pressure in the posterior chamber may not produce angle closure before the aqueous breaks through the pupillary block and resumes its normal flow pattern. Angle closure due to pupillary block can present as an acute glaucoma, a subacute (intermittent) glaucoma, a chronic glaucoma, or by a combined mechanism.

PEARL... Angle closure due to pupillary block can present as an acute glaucoma, a subacute (intermittent) glaucoma, or a chronic glaucoma, or by a combined mechanism.

Acute Angle Closure

Many factors can favor the development of an acute attack. (Table 16-2). Whether or not pupillary block

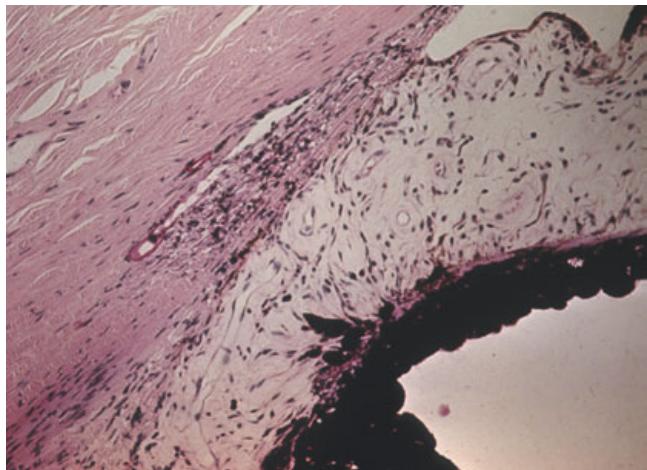


FIGURE 16-2 Light micrograph of the anterior chamber angle from an eye with a history of acute angle closure. The peripheral iris is adherent to the trabecular meshwork.

develops and produces angle closure depends on a shallow anterior chamber,⁴¹ a short axial length of the eye,^{42,43} increased lens thickness,^{44,45} forward position of the lens,⁴⁶ and how tightly the iris hugs the lens. Lowe found that PACG was most likely to occur in cases with an anterior chamber depth between 1.5 and 2.0 mm.⁴⁷ Acute closure of the angle occurs when iris bombé becomes extensive enough to cover the entire trabecular meshwork (Fig. 16-2). Because aqueous humor has no access to the outflow system, the intraocular pressure (IOP) can rise 20 to 40 mm Hg within minutes.

Several circumstances can precipitate acute angle-closure glaucoma in eyes that are so predisposed. These include:

Physiologic mydriasis (dark room, movie theater)

Pharmacologic mydriasis (mydriatics, cycloplegics including use of preoperative intramuscular atropine)

Sudden anxiety (pain, fear, trauma, emotional disturbance)

Systemic medications that may produce mild mydriasis (sleep medication, tranquilizers, cold medications, eye drops with vasoconstrictors, a variety of medications to treat upper respiratory illness, and anticholinergics)

Intermittent (Subacute, Subclinical) Angle Closure

Intermittent angle closure attacks may occur under conditions similar to acute angle closure, but undergo spontaneous resolution. The IOP may rise to high levels, but before it causes more than mild symptoms, the aqueous humor breaks through the pupillary block and once again flows through the pupil into the anterior chamber. The peripheral iris falls back and the aqueous regains access to the trabecular meshwork. This condition is doomed to

TABLE 16-2 FACTORS FAVORING AN ACUTE ANGLE-CLOSURE ATTACK

Narrow anterior chamber angle
Shallow anterior chamber depth
Short axial length of globe
Small corneal diameter
Increased thickness of lens
Physiologic mydriasis
Pharmacologic mydriasis
Systemic medications

recur until a laser iridotomy is performed to provide an alternate pathway for aqueous flow. Without this, patients with intermittent angle closure may ultimately develop an acute attack or a symptomatic form of intermittent angle closure. Others may go on to develop chronic angle closure.

Chronic Angle Closure

Chronic angle closure with pupillary block can occur in several different patterns. In some eyes, apposition begins deep within the narrowed angle and then spreads anteriorly to eventually cover first the posterior and then the anterior meshwork.⁴⁸ Lowe aptly characterized this chronic progression as creeping glaucoma because more and more of the angle becomes zippered closed with PAS, causing the glaucoma to become increasingly difficult to control.⁴⁹ In the past, treatment of elevated IOP with increasingly potent miotics could exacerbate the glaucoma due to the tendency of these drugs to move the ciliary body forward, tighten the iris across the lens, and increase the pupillary block.⁵⁰

In other eyes, apposition begins with the peripheral iris closing down on the midtrabecular meshwork or at the level of Schwalbe's line.⁵¹ Here, chronic angle-closure glaucoma results from appositional closure without PAS, but the angle will open again when the pupillary block subsides. However, particularly with associated inflammation, parts of the angle will eventually begin to close with PAS, beginning with the superior angle.⁵² Closure of one half to two thirds of the angle with PAS results in permanent elevation of IOP.

Combined Mechanism Glaucoma

This refers to cases with both open-angle and angle-closure glaucoma. Many of these eyes present with a diagnosis of pupillary-block glaucoma, but iridotomy fails to bring the glaucoma under control. Many represent a form of chronic angle-closure glaucoma where the meshwork has been damaged by the intermittent or chronic trauma from the obstructing peripheral iris. The iridotomy may halt further angle closure, but residual trabecular pathology is sufficient to produce chronic glaucoma. In either situation, the residual open-angle component is treated with conventional medical therapy and may even respond to laser trabeculoplasty.

SPECIAL CONSIDERATION

Combined mechanism glaucoma refers to eyes with both pupillary block angle-closure glaucoma and open-angle glaucoma.

TABLE 16-3 DIAGNOSIS OF ACUTE ANGLE-CLOSURE GLAUCOMA

<i>Symptoms</i>	<i>Signs</i>
Pain	Shallow anterior chamber, convex iris
Nausea, vomiting	Iritis, flare, ocular congestion
Blurred vision	Mid-dilated pupil, poor reaction
Halos	Epithelial edema Glaukomflecken Closed anterior chamber angle with PAS Optic nerve head edema

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute Angle-Closure Glaucoma

The classical picture of acute angle-closure glaucoma is dramatic, due to the rapid and severe rise in IOP (Table 16-3). Many patients experience severe ocular and maxillary pain, mediated by the fifth cranial nerve, and a penetrating brow ache. In some cases, the pain may extend to the head, sinuses, and teeth. We have seen one patient who mistakenly had three teeth extracted for this pain. Other symptoms include nausea and vomiting, produced by stimulation of the fifth cranial nerve and its connections with the descending branch of the longitudinal fasciculus of the tenth nucleus. Bradycardia and sweating may occur as a result of the oculocardiac reflex.

Blurred vision generally results from corneal edema when the increased IOP forces aqueous humor into the cornea. This can also cause the patient to note colored haloes around lights, with the red part of the spectrum being more peripheral. Corneal edema can often stimulate lacrimation.

The anterior chamber is very shallow, and the iris may be obviously bowed anteriorly. Acute iritis, leading to congestion of the iris and hyperemia of the conjunctival and episcleral vessels, can also occur (Fig. 16-3A), along with cells and flare in the anterior chamber and occasional keratic precipitates. The accompanying excess protein in the aqueous humor predisposes to the formation of PAS across an already narrowed angle (Fig. 16-3B) as well as posterior synechiae.

Continued high IOP may produce ischemia and temporary paralysis of the pupillary sphincter. Thus the pupil is usually fixed in the mid-dilated position (Fig. 16-3C). Eventually, ischemic necrosis of the pupil will occur, leading to a permanent mydriasis and atrophy of the iris stroma (Fig. 16-3C). A cataract often develops after acute angle closure and can occur even if the pressure is only moderately elevated (35–45 mm Hg). Irregular, small, gray-white anterior subcapsular lens, opacities, or "glaukomflecken," often appear within the

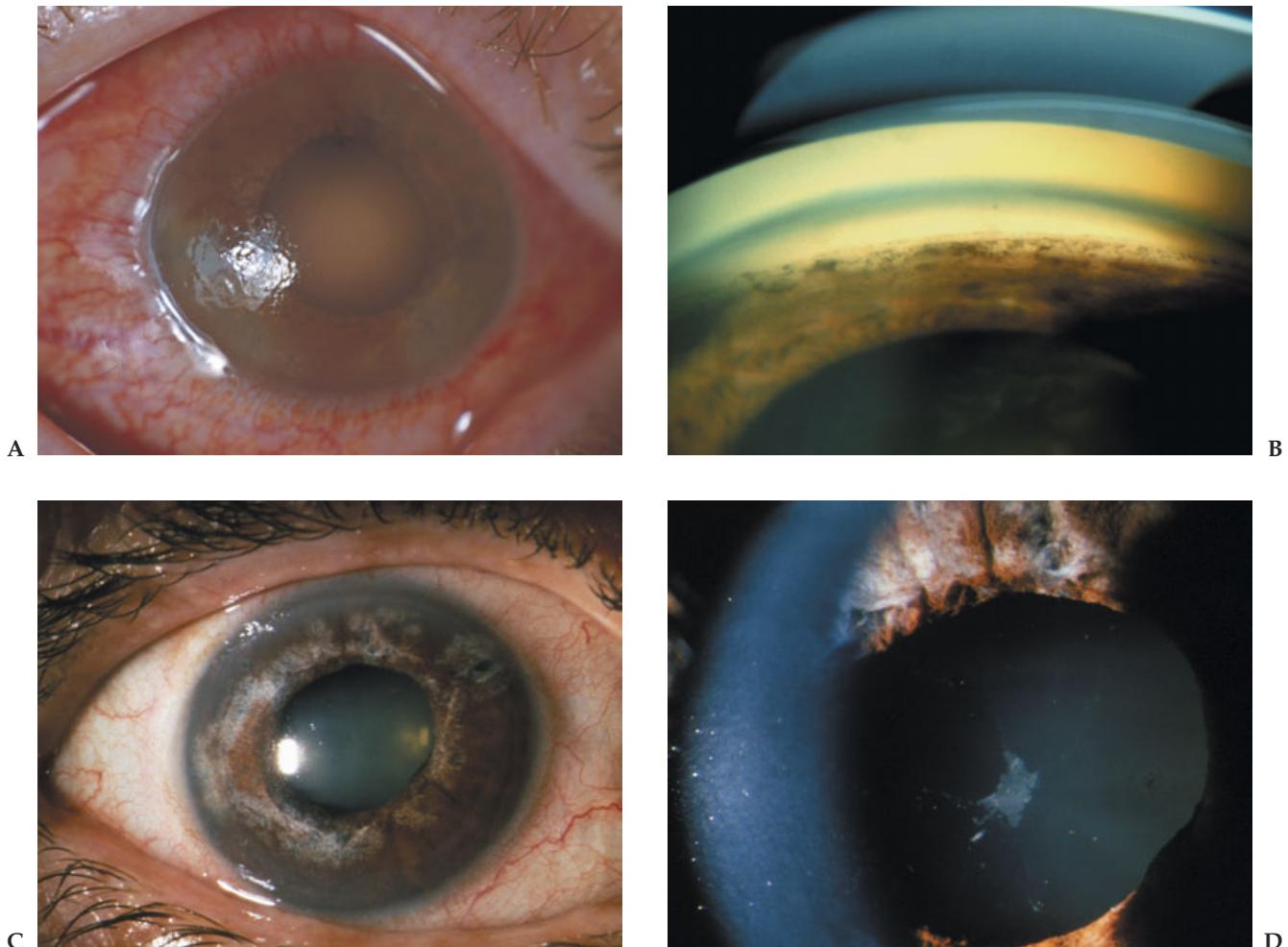


FIGURE 16-3 (A) Conjunctival injection, corneal edema, and a mid-dilated pupil are common signs of an acute angle-closure glaucoma attack. An eye with a history of previous attacks can demonstrate (B) focal regions of tentlike PAS; (C) iris atrophy with a fixed, mid-dilated pupil; and (D) glaukomflecken, coalescing here into a larger, central opacity. [(A) Courtesy of Kenneth C. Swan, M.D.]

pupil (Fig. 16-3D). Examination of the posterior pole may reveal striking venous pulsations, as well as edema of the optic nerve head.

Gonioscopic proof that the angle is closed in the involved eye is the most important sign of acute angle-closure glaucoma. If corneal edema interferes with adequate visualization of the angle in the involved eye, then the fellow, uninvolved eye should be carefully examined and will usually reveal a narrowed anterior chamber angle. If the angle is open in both eyes, then one must consider other causes of acute glaucoma, but where there is no pupillary block (Table 16-4). The differential diagnosis of primary pupillary block glaucoma includes primary nonpupillary block glaucoma (plateau iris syndrome) and secondary forms of pupillary block and nonpupillary block angle-closure glaucoma.

PEARL... If corneal edema interferes with gonioscopy of an eye with suspected acute angle closure, the fellow eye will usually reveal a narrowed anterior chamber angle.

TABLE 16-4 ACUTE GLAUCOMA IN EYES WITH OPEN ANGLES

- Acute uveitis, including Posner-Schlossman syndrome
- Heterochromic iridocyclitis
- Pigmentary glaucoma
- Steroid-induced glaucoma
- Neovascular glaucoma

Intermittent Angle-Closure Glaucoma

Patients with intermittent angle-closure glaucoma present with the same signs and symptoms as those associated with acute angle-closure glaucoma. However, they are generally milder and resolve spontaneously. Examination reveals a shallow anterior chamber and a narrowed or closed chamber angle, with or without PAS, even between attacks. The IOP is often normal between attacks but may be increased by provocative testing, as discussed in the following text. Careful questioning often reveals that the attacks occur when the patient is in a darkened room, such as in a movie theater or at a bar.

Case History: Mr. And Mrs. C went ballroom dancing every Saturday night. After 1 hour, Mrs. C always developed pain in the left eye with mild redness, which disappeared soon after returning home. A mydriatic provocative test caused the IOP to rise from 15 mm Hg to 42 mm Hg in 45 minutes. The angle, originally slitlike, closed after mydriasis.

Chronic Angle-Closure Glaucoma

Patients with chronic angle-closure glaucoma typically have no symptoms, and the diagnosis is often mistaken for open-angle glaucoma unless careful gonioscopy is performed.⁵³ In early cases, closure may be only appositional. With time, broad PAS eventually form and the angle circumference closes from above downward,⁵² accompanied by pressure that is increasingly difficult to control (Fig. 16-4).

PITFALL... Situations where an occludable angle mistakenly appears open by gonioscopy include:

1. Angle open only to the anterior trabecular meshwork
2. Unintentional indentation gonioscopy
3. Undetected intermittent angle closure
4. Pigmented Schwalbe's line mistaken for trabecular meshwork

Much more difficult to diagnose are those cases where the angle mistakenly appears to be open by gonioscopy. This can occur under four circumstances:

1. *Angle open only to the anterior trabecular meshwork.* In this situation, already described as creeping glaucoma, gonioscopy reveals a narrow approach to the trabecular meshwork. However, pressure gonioscopy reveals that only the anterior meshwork is visible and the posterior meshwork, through which most filtration occurs, is occluded with synechiae or by appositional closure. This is probably the most common cause of overlooked chronic angle-closure glaucoma.

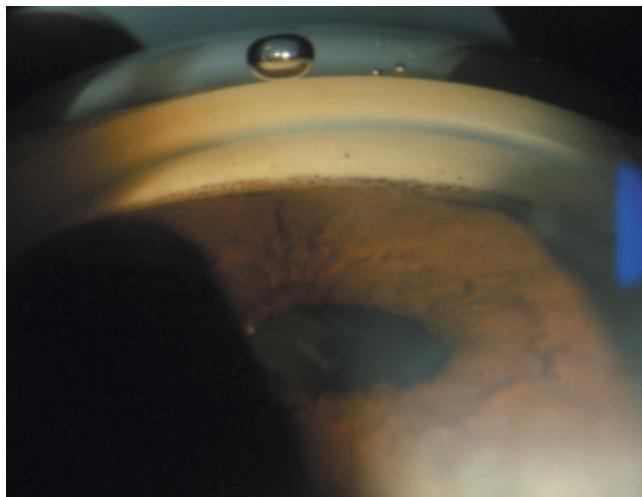


FIGURE 16-4 Broad PAS in a patient with chronic angle-closure glaucoma.

2. *Unintentional indentation gonioscopy.* Here there is appositional closure, but gonioscopy causes the angle to open without the examiner intending to do so. This is more likely to occur with the four-mirror lens, but it can occur with any goniolens whenever the examiner pushes too hard on the cornea.
3. *Undetected intermittent angle closure.* This may occur without progressing to an acute attack, but it may lead to formation of PAS. If the eye is examined during a period when the angle is not closed, the examiner may mistakenly conclude that the angle is narrow, but not occludable. Some of these cases may also have functional meshwork damage from intermittent appositional closure.
4. *Pigmented Schwalbe's line mistaken for trabecular meshwork.* Here, one may erroneously get the impression that all of the angle structures are visible. However, pressure gonioscopy or an iridotomy (Fig. 16-5A,B) generally reveals that what appeared to be trabecular meshwork was really pigmented Schwalbe's line. What appeared to be ciliary body was really anterior trabecular meshwork, and the relatively unpigmented area between was believed to be scleral spur.

Many of these patients frequently show an initial favorable pressure response to medical therapy, but soon the pressure goes out of control, with large fluctuations in IOP that defy medical management.⁵³ As more and more medication is used, more and more synechial closure occurs because of the compromised angle. The success of medical treatment in this situation depends heavily on early diagnosis and laser iridotomy.

Cases of angle closure with obvious PAS are more easily diagnosed. However, one must carefully differentiate eyes in which the PAS was caused by pupillary block

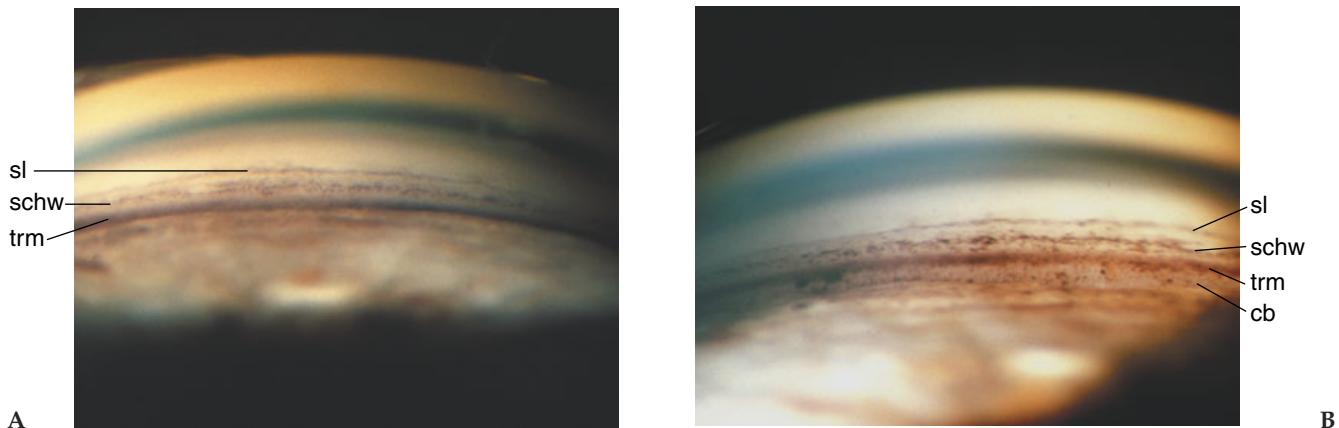


FIGURE 16-5 (A) Goniophotograph of an angle wrongly interpreted as being open to the ciliary body. What appears to be trabecular meshwork is actually pigmented Schwalbe's line. (B) The true relationships are easily seen following a laser iridotomy. sl, Sampaolesi's line; schw, Schwalbe's line; tm, trabecular meshwork; cb, ciliary body. (Courtesy of Mary Lynch, M.D., and Reay Brown, M.D.)

from those in which it was not. Only the former cases are amenable to laser iridotomy.

DIAGNOSTIC TECHNIQUES FOR PUPILLARY BLOCK

Flashlight Test

The width of the anterior chamber angle can be crudely estimated by holding a penlight at the temporal side of the eye so that the light beam enters the eye through the temporal cornea, crosses the anterior chamber parallel to the iris plane, and exits the eye near the inner canthus. If the iris is bowed forward (iris bombé), the temporal iris will light up while the nasal iris will be left in the shadow. Patel and coworkers⁵⁴ found that this test had a low sensitivity (28.9%) for predicting the presence of an occludable (slit to closed) angle but was highly specific (99.4%).

Van Herick Test

In this technique, the slit beam of the biomicroscope is directed at the peripheral cornea, using the blue light to avoid undue illumination and miosis. If the chamber depth is less than one fourth the corneal thickness, it is a grade I angle or less.⁵⁵ The sensitivity and specificity of this test are 61.9% and 89.3%, respectively. It is, therefore, of limited use in screening eyes for occludable angles. Neither this nor the flashlight test can substitute for gonioscopy.^{56,57}

Gonioscopy

Gonioscopy allows the examiner to determine whether the anterior chamber angle is open, narrowed, and occludable, or closed. There are many ways to grade the anterior chamber angle, one of the commonest of which

is the Shaffer classification (see Chapter 5). By this technique the angle approach is graded from 0 (closed) to IV (wide open). Any angle that is graded slit or I is considered to be occludable.

Only a small percentage of the general population in the U.S. and Europe will develop a shallow anterior chamber whose angle is narrower than usual. Grade I angles have been demonstrated in only 0.64% of an aging population.⁵⁵ The presence of an extremely shallow anterior chamber or narrow angle, with an angle approach less than 20 degrees, should alert the examiner to the eye's potential for angle closure. Gonioscopy with either the Goldmann or four-mirror lens can help the examiner estimate the angle approach and determine the type of glaucoma present. As already mentioned, inadvertent indentation gonioscopy, particularly with the four-mirror lens, may cause the clinician to overestimate the width of the angle.

Indentation Gonioscopy

There is a direct relationship between the degree of synechial closure and residual glaucoma after iridotomy. Indentation gonioscopy with the four-mirror gonioscopy lens can help reveal the presence and extent of PAS and differentiate between appositional contact and synechial closure.⁵⁸

PEARL... Indentation gonioscopy can help the clinician differentiate between appositional contact and synechial angle closure.

Indentation gonioscopy may also help the clinician diagnose chronic angle-closure glaucoma. In such cases, one may see the anterior trabecular meshwork by conventional gonioscopy but fail to appreciate appositional

closure to the posterior meshwork and scleral spur. With indentation gonioscopy, the clinician can open the angle to its fullest extent and thereby reveal the presence of appositional closure. Such an angle might respond well to laser iridotomy. If, on the other hand, much of the angle circumference is closed with PAS, then laser iridotomy will have limited benefit.

Ultrasound Biomicroscopy

Ultrasound biomicroscopy not only provides a view of the anterior chamber angle, it may also reveal clues to the diagnosis of various types of glaucoma. It allows one to see the position of the ciliary body and its processes as well as the various structures in front of and behind the iris root.^{59,60} In combination with tonometry, ultrasonography can provide 88% sensitivity and 92% specificity for the diagnosis of angle-closure glaucoma (Fig. 16.7).⁵⁷

PROVOCATIVE TESTING IN ANGLE-CLOSURE GLAUCOMA

Approximately 5% of the U.S. population has a shallow anterior chamber with a narrow approach to the angle. A small proportion of these individuals are at risk of developing angle-closure glaucoma sometime during their life. Because laser iridotomy is a fairly safe and simple procedure that can eliminate this risk, there is clearly an interest in identifying these individuals at an early stage and treating them prophylactically.⁶¹

One tool for identifying these “at risk” eyes is the angle-closure provocative test. These can be divided into two groups, based on the method by which they potentially provoke angle closure and elevate IOP.⁶² Some are physiological tests that mimic natural events, whereas others use an artificial intervention.

Darkroom Provocative Test

In this test, the patient is placed in a dark room to induce physiological dilatation of the pupil. This may provoke angle closure, either by enhancing pupillary block or by mechanically crowding the peripheral angle with folds of iris.⁶³ Following a slit-lamp exam and IOP measurement, the patient is placed in a dark room for 40 to 60 minutes. The IOP is then remeasured. A rise in IOP of 8 mm Hg or more is considered a positive result.

When performing this test, very elderly patients with senile miosis may need to stay in the dark for a longer period of time because they dilate much more slowly than younger people. In addition, the patient must be kept awake, either by a companion or the technician because physiological miosis might occur if the patient falls asleep. Finally, when the patient is re-examined after the test, this must be done very quickly and under dim illumination, to minimize the chance of the pupil constricting in the light and decreasing the pressure.

Prone Provocative Test

For this test, the patient’s head is placed face down in a horizontal orientation for a period of 40 to 60 minutes. With the face parallel to the floor, the lens–iris diaphragm may shift forward, enhancing the likelihood of pupillary block.⁶⁴ The patient can be comfortably seated at a desk or table and on a chair that is sufficiently high to allow the forehead to rest on the back of the hand or forearm (Fig. 16–6). The test is conducted in an analogous manner to the dark room test above. Here, too, the patient must be kept awake.

Dark-Room, Prone Provocative Test

Conducting the prone provocative test in a dark room combines these two tests. Given that some patients will respond positively to one test but not the other,⁶⁵ this increases the chance of getting a positive result.

Mydriatic Provocative Test

This test utilizes either sympathetic agonists or cholinergic antagonists to dilate the pupil. The sympathomimetics stimulate the dilator muscle of the iris and include either direct-acting agents such as phenylephrine (Neo-Synephrine) or indirect-acting agents such as hydroxyamphetamine (Paredrine).⁶⁶ The cholinergic antagonists block constriction of the iris sphincter muscle and include tropicamide, homatropine, and atropine. The short-acting tropicamide is most frequently used for this test.⁶¹

For these pharmacological tests, the patient’s IOP is measured, the dilating agent is instilled, and then the patient is checked every 10 to 15 minutes to detect any rapid rise in IOP. When the pupil dilates approximately 4 to 5 mm, the iris will have thickened and will rest on the crystalline lens where the anterior lens curvature begins to recede. This is the best time to re-measure the pres-



FIGURE 16-6 The prone provocative test.

sure. Some practitioners simply check the patient 45 to 60 minutes after instilling the mydriatic.

The clinician must remember that *any* rise in pressure less than 8 mm Hg at the end of the test might indicate the beginning of an ascending pressure curve and a potentially positive result. When this happens, the IOP should be checked again in 15 to 30 minutes. It should also be remembered that cycloplegia alone can produce a significant rise in IOP in eyes with compromised trabecular function. Therefore, any potentially positive test should always be accompanied by repeat gonioscopy to document angle closure.

PITFALL... Any potentially positive provocative test should always be accompanied by repeat gonioscopy to document angle closure and rule out other causes of elevated IOP.

The Clinical Role of Provocative Tests

Prospective studies have shown that, without treatment, at least 50% of fellow eyes from patients with acute angle-closure glaucoma will develop acute angle closure within 5 years.⁶⁷ Although it is reasonable to expect a significant number of these fellow eyes to have positive provocative tests, results in reality are much lower than this. Moreover, some eyes will yield a positive response to one test but a negative one to several others. Finally, even some eyes with patent iridotomies will have a pressure rise high enough to constitute a positive result when provoked with one of these tests.

In one multicenter, prospective study, 129 eyes deemed at risk for developing angle-closure glaucoma were evaluated by a number of provocative tests.⁶⁸ The patients were then followed prospectively with no intervention for up to 6 years. Twenty-five eyes had positive provocative tests, but only six of these actually developed angle closure. Conversely, 19 of 25 eyes that did develop angle closure had had a negative dark room, prone provocative test. Thus the provocative test had both low sensitivity and specificity for identifying eyes capable of developing angle closure. In the Baltimore Eye Survey, 4,870 subjects had their eyes dilated, but none developed acute angle-closure even though 38 patients were later found to have slit to closed angles.⁵⁴

In spite of these limitations, there are times when the provocative test provides useful supportive evidence for the need of an iridotomy, as in the following examples:

The patient presents with a history suggestive of intermittent angle-closure attacks and a gonioscopically narrow angle that is not convincingly occludable.

The angle is narrowed and possibly occludable (Shaffer Grade I) but the ophthalmologist is unsure that the angle is occludable, or the patient is unsure about undergoing an iridotomy. This is especially important if there is a family history of glaucoma.

The patient is extremely anxious about the discovery of narrow angles that are possibly occludable—especially if the patient travels frequently or if he or she is dependent on medications that are contraindicated in angle-closure glaucoma.

In each of these examples the ophthalmologist and patient may elect to proceed with an iridotomy, if the test is positive.

MANAGEMENT OF ANGLE-CLOSURE GLAUCOMA WITH PUPILLARY BLOCK

Medical Therapy

Medical treatment is used to lower the IOP, alleviate pain, and clear the cornea enough to allow a laser iridotomy. Medical treatment consists of beta-adrenergic blocking agents that usually take effect in 20 to 30 minutes, and a topical carbonic anhydrase inhibitor (CAI). Topical alpha-2 agonists may lower the IOP and lessen the chance of bleeding during the procedure. Although these agents can cause slight mydriasis in the normal eye, they are not likely to affect the dilated fixed pupil in the eye with an acute attack.

Pilocarpine, 1 or 2%, can be administered every 10 to 15 minutes for 1 to 2 hours to open the angle,⁶⁹ increase aqueous outflow, lower the IOP, and stretch the iris in preparation for the iridotomy. However, it will fail in the presence of persistent iris ischemia. Greater strengths of pilocarpine or cholinesterase inhibitors may aggravate ciliary congestion, and are generally avoided. An oral CAI (methazolamide 100 mg or acetazolamide 500 mg) should also be administered to help lower the IOP, but this may take up to 2 hours. A long-acting capsule of acetazolamide can provide a sustained decrease in IOP.

In many instances, topical and oral medications are unable to lower the IOP. Therefore, every effort should be made to give the patient an oral osmotic agent. Osmoglynn (Alcon) or oral glycerine, 2ml/kgm B.W. on ice may effectively lower the pressure in 20 to 40 minutes. If the patient is nauseated, this should be given in small increments over a period of 10 to 15 minutes.

In cases where the patient has so much nausea and vomiting that oral osmotic agents cannot be used, intravenous administration of 500 mg acetazolamide may be helpful. Otherwise, it is preferable to give 20% mannitol in a dose of 2 to 7 mL per kilogram of body weight over 30 minutes. In most cases, 150 to 200 mL of 20% mannitol given at the rate of 60 drops per minute will rapidly lower the IOP and help clear the cornea.

Ancillary steps to help reduce the IOP include the use of topical prednisolone 1% every hour to reduce intraocular inflammation. In addition, the clinician can physically deepen the anterior chamber by intermittently depressing the central cornea with a moist cotton swab or blunt instrument. This will displace aqueous humor

toward the periphery of the anterior chamber, open the anterior chamber angle, and reduce the IOP.⁷⁰

Laser Therapy

Laser iridotomy is the definitive treatment for pupillary-block angle-closure glaucoma. It is best performed when the eye is quiet, the cornea is clear, and there is no intraocular inflammation or uveal congestion. Unfortunately, this is rarely the case when a patient presents with acute congestive glaucoma.

If the cornea is clear and there is relatively little intraocular inflammation, then the surgeon should proceed immediately with a laser iridotomy (see Chapter 41). In most circumstances, a patent iridotomy with the neodymium:YAG (Nd:YAG) laser can usually be achieved using settings of 6 to 8 millijoules (mJ) with a pulse train of 2 through an iridotomia contact lens.

On the other hand, if the medical therapies described above successfully break an acute attack, the eye will often have considerable residual intraocular inflammation, even though the cornea may appear clear. In such a case, it is desirable to defer the laser iridotomy until the following day, maintaining the patient on topical glaucoma drops, prednisolone 1%, and oral CAIs overnight.

In rare cases, this management protocol will fail or may not be available. In others, the cornea may not clear adequately to allow a reliable iridotomy. If this occurs, the pupil can be "peaked" with a partial pupilloplasty. Here, low power applications of argon laser over 1 to 2 clock hours may displace the pupil margin sufficiently to temporarily break the pupillary block.^{71,72} Another alternative is to perform peripheral iridoplasty with the argon laser. This may contract the peripheral iris and pull it away from

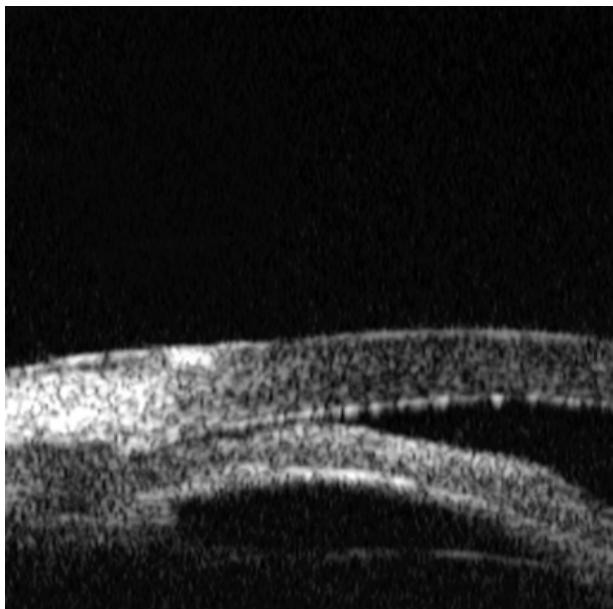
the trabecular meshwork. Treatment settings include use of a 500 μm spot for 0.2 to 0.5 seconds with 200 to 700 mW.^{71,73,74}

As with successful medical therapy, neither of these alternative laser treatments provides permanent relief from pupillary block. These must still be followed by a definitive laser iridotomy.

Unfortunately, laser iridotomy for acute angle-closure glaucoma is not always successful.^{75,76} Playfair and Watson found that treatment of acute angle-closure glaucoma with an iridotomy alone or in combination with miotics would control the IOP in 77% of cases if there were no initial visual field loss. This dropped to 29% if there was initial field loss.⁷⁷ If the glaucoma is due to pupillary block and appositional closure, the angle should open wider following treatment (Fig. 16-7A,B), although the central chamber itself may not change in depth.^{78,79} Failure of the anterior chamber angle to open following laser iridotomy usually results from extensive PAS, or if the angle closure was not caused by pupillary block. Additional iridotomies will not remedy this situation.

Although one can attempt to predict the presence and extent of PAS with indentation gonioscopy, this is not always possible or reliable during the acute attack. Laser iridotomy is sufficiently safe that a trial with laser iridotomy followed by medical therapy is generally quite appropriate before proceeding to more invasive procedures, such as a trabeculectomy.

In some eyes, the angle will open adequately following laser iridotomy, but the IOP remains elevated. This is usually the result of trauma to the trabecular meshwork or a combined mechanism where there is an inherently reduced aqueous outflow. Such eyes can be treated by



A



B

FIGURE 16-7 (A) Ultrasound biomicroscopy of an eye with pupillary block before and (B) after laser iridotomy. Note that the angle is wider and the iris has lost its bombé configuration.

conventional laser trabeculoplasty before proceeding to a filtering procedure.

Angle-closure glaucoma, like open-angle glaucoma, is a bilateral disease. Therefore, the fellow eye will almost always have an occludable angle and should receive a laser iridotomy once the first eye is stable. Unfortunately, iridotomy in even the fellow eye may not prevent the eventual need for therapy. In one study, 50% of patients with PACG treated with bilateral peripheral iridectomies required additional therapy of some type in the involved eye, and 25% required treatment in the noninvolved eye. Many of these cases were believed to have combined-mechanism glaucoma.⁸⁰

Acute Angle-Closure Glaucoma

A patient who suffers an acute attack of pupillary-block glaucoma is in great distress. The IOP is markedly elevated, and the cornea may be edematous. This makes it difficult to focus the laser on the iris and often precludes an immediate laser iridotomy. Furthermore, the patient may have nausea, and ingestion of any oral medications will more than likely cause the patient to vomit. Typically, these patients arrive in the office on a Friday afternoon. Initial treatment is always medical to lower the IOP, followed by a laser iridotomy.

Intermittent Primary Angle-Closure Glaucoma with Pupillary Block

Patients who have intermittent mild attacks of pupillary-block angle closure can be identified by their history and the presence of an occludable anterior chamber angle. These eyes should be treated with a prophylactic laser iridotomy.

If the patient is reluctant to undergo laser treatment, or if the examiner is uncertain of the diagnosis, the clinician can educate the patient about the warning signs of acute angle closure and the need to seek immediate attention should they develop. Such cases require weighing the benefits and risks of a prophylactic laser iridotomy against the patient's mental anguish and constant fear of an acute attack. This is of particular concern for the patient who travels extensively. A provocative test may be helpful in such cases.

Chronic Angle-Closure Glaucoma

As described above, chronic angle-closure glaucoma results from gradual synechial closure of the angle secondary to pupillary block. Here, too, the treatment of choice is a laser iridotomy. However, this alone is often not enough to control the IOP, and medical therapy will be required. Even then, many cases ultimately require a filtering operation, particularly if there is visual field loss.^{75,76,81}

Prophylactic Laser Iridotomy

A laser iridotomy is *always* indicated in the fellow eye of a patient who suffered an acute angle closure in the first eye. Other indications include an angle that is so narrow that a

provocative test is dangerous and unnecessary.⁸² Such an angle would be narrowed to a slit or closed, or would require indentation gonioscopy to view the scleral spur. Another situation for prophylactic iridotomy is the presence of PAS in an eye with a narrow angle. Other considerations that may influence the decision to perform prophylactic laser iridotomy include a family history of angle-closure glaucoma, the need for frequent pupillary dilatation, such as someone with diabetic retinopathy, and age over 80.

SECONDARY ANGLE-CLOSURE GLAUCOMA WITH PUPILLARY BLOCK

Unlike primary angle closure, secondary angle closure with pupillary block is usually unilateral and due to several existing ocular conditions listed in Table 16–5.

POSTERIOR SYNECHIAE

Adhesions between the pupillary margin of the iris and the underlying lens may occur following intraocular inflammation, such as might occur with uveitis and trauma. Less commonly, pseudophakic pupillary block due to posterior synechiae can occur with a posterior chamber implant.

Delayed formation of the anterior chamber following intraocular surgery can encourage the development of posterior synechiae. When aqueous formation resumes, it is trapped in the posterior chamber, causing iris bombé and angle-closure glaucoma with a sudden, dramatic rise in the IOP. Prompt and vigorous mydriasis may break fresh synechiae, and anti-inflammatory agents can help prevent their formation. If this fails, then a laser iridotomy is required.

PUPILLARY BLOCK FOLLOWING USE OF MIOTICS

Parasympathomimetic agents relax the lens zonules, producing a forward shift of the iris-lens diaphragm. In such cases, the anterior chamber will shallow, leading to relative pupillary block and angle closure. Miotic-induced angle-closure glaucoma may present with chronic angle closure that can be diagnosed by gonioscopy. These eyes are often predisposed to angle closure even before the miosis and should be treated with a laser iridotomy.

TABLE 16-5 CAUSES OF SECONDARY ANGLE-CLOSURE GLAUCOMA DUE TO PUPILLARY BLOCK

Posterior synechiae
Miotics
Pseudophakia (Chapter 28)
Anterior hyaloid face
Intraocular gas and silicone oil (Chapter 27)
Lens-induced (Chapter 25)
Retinopathy of prematurity (Chapter 27)

PSEUDOPHAKIC AND APHAKIC (VITREOUS) BLOCK GLAUCOMA (CHAPTER 28)

Pupillary block can occur with either anterior or posterior chamber lens implants.⁸³ However, it occurs much more frequently with the anterior chamber implants, and their use should always be accompanied by a peripheral iridectomy or a postoperative laser iridotomy.

Eyes operated on in the pre-implant days were occasionally subject to acute pupillary block by the anterior hyaloid face. The signs and symptoms of this condition are similar to those of primary pupillary-block glaucoma (see Table 16–2). The treatment is also the same.

PUPILLARY BLOCK FOLLOWING PARS PLANA VITRECTOMY AND INTRAVITREAL GAS (CHAPTER 27)

Elevated IOP is the most common complication of fluid–gas exchange with long-acting gases. In a prospective study, Mittra et al found that 52% of such patients had an IOP greater than 25 mm Hg and 29% an IOP greater than 30 mm Hg.⁸⁴ The IOP elevation can result from pupillary block following expansion of the gas bubble. It can also occur without pupillary block, due to swelling and anterior rotation of the ciliary body. In many cases, these two entities probably coexist. The glaucoma can be treated by aspiration of the gas at the slit-lamp, but most cases will respond to medical therapy.

Other causes of secondary pupillary-block glaucoma include lens-induced glaucoma (Chapters 20 and 25); malignant glaucoma (Chapter 28); and retinopathy of prematurity (Chapter 27) and nanophthalmos.

PRIMARY ANGLE-CLOSURE GLAUCOMA WITHOUT PUPILLARY BLOCK

In a small percentage of cases, one may encounter acute angle-closure glaucoma that is not relieved by a laser iridotomy or that recurs at a later date despite the presence of a patent iridotomy.^{85,86} Although we now have insight into the pathophysiology of this condition, discussed in the following text, there does not appear to be any external cause, and we categorize it as a primary form of angle-closure without pupillary block.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The classical picture consists of an eye with plateau iris configuration.⁸⁷ The iris plane is flat with a normal central anterior chamber depth. However, the peripheral iris comes extremely close to the angle wall as it inserts into the ciliary body. Unlike pupillary block, there is no iris bomé, yet the angle approach is close to being a slit, and the potential for angle closure is apparent. Ultrasound biomicroscopy demonstrates anterior rotation of the ciliary

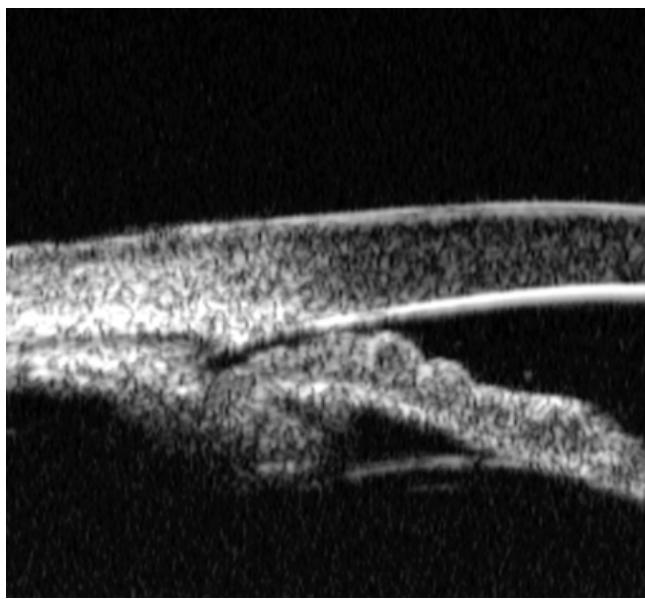


FIGURE 16-8 Plateau iris configuration. The ciliary body and processes are anteriorly rotated and push the peripheral iris close to the angle wall, leaving the central iris plane flat.

body and ciliary processes that appear to push the peripheral iris close to the angle wall (Fig. 16–8). Plateau iris configuration is more common than generally recognized.

Wand and coworkers⁸⁸ suggested that plateau iris configuration be considered a separate entity from plateau iris syndrome. This resembles plateau iris configuration except that there is glaucoma despite the presence of a patent iridotomy. The narrowed angle is predisposed to closure when the pupil dilates spontaneously or after instillation of mydriatic agents.^{89,90}

Many, if not most, cases of apparent plateau iris syndrome are cured by laser iridotomy, indicating that pupillary block may play a significant role in the development of angle closure in these cases. Therefore, diagnosis of this entity requires that the glaucoma persist despite the presence of a patent iridotomy.

PEARL... The diagnosis of plateau iris syndrome requires that the glaucoma persist despite the presence of a patent iridotomy.

The differential diagnosis includes pupil block glaucoma with an incomplete iridotomy, multiple cysts of the iris or ciliary body, ring melanoma of the iris, malignant (ciliary block) glaucoma, and combined-mechanism glaucoma.

MANAGEMENT

Treatment of plateau iris syndrome (where a patent laser iridotomy already exists) consists of using miotics to constrict the pupil, reduce peripheral iris folds in the angle,

and pull the iris away from the angle wall. If this fails, iridoplasty can be performed to widen the angle.^{89–95} This technique uses laser burns around the peripheral iris to contract the iris stroma between the site of the burn and the angle wall and widen the angle. Pilocarpine 4% is applied before treatment to stretch the iris. Using 500 µm spots for 0.5 second and with 200 to 400 mW, 24 to 36 applications are made in the peripheral iris over 360 degrees. These burns are precisely placed by aiming the laser beam through an iridotomies lens or a Goldmann gonioscopy lens at the most peripheral portion of the iris.⁹⁵ This produces immediate iris contraction, deepening of the anterior chamber at the burn site, and widening of the angle approach.

Complications of iridoplasty include iritis and dispersion of pigment and iris debris into the aqueous humor. If the anterior chamber is extremely shallow, corneal endothelial burns can occur. These usually disappear within several days, but corneal decompensation can occur. A postoperative rise in IOP is common and can be avoided or minimized by instillation of 1% apraclonidine hydrochloride or 0.2% brimonidine. Postoperative topical prednisolone is routinely used to manage inflammation.

SECONDARY ANGLE-CLOSURE GLAUCOMA WITHOUT PUPILLARY BLOCK

Angle-closure glaucoma without pupillary block more commonly follows intraocular surgery or other precipitating ocular conditions. In such cases, the peripheral iris is forced into apposition with the trabecular meshwork and peripheral cornea. Shields has suggested that the peripheral iris may be either “pulled” (anterior mechanism) or “pushed” (posterior mechanism) into this position.⁹⁶

ANTERIOR PULLING MECHANISMS

In most of these cases, the glaucoma is caused by PAS that obstruct the angle (Table 16–6). These can result from intraocular inflammation, neovascularization of the angle, or diseases of the surrounding tissues.

TABLE 16-6 SECONDARY ANGLE-CLOSURE GLAUCOMA WITHOUT PUPILLARY BLOCK: ANTERIOR PULLING MECHANISMS

Peripheral anterior synechiae
Neovascular glaucoma (Chapter 21)
Iridocorneal endothelial syndrome (Chapter 22)
Posterior polymorphous dystrophy
Epithelial downgrowth (Chapter 28)
Aniridia (Chapter 17)
Iridoschisis

Peripheral Anterior Synechiae

The PAS associated with inflammation of the anterior segment may be scattered or continuous. In contrast to the posterior adhesions of chronic angle-closure glaucoma, PAS result from contraction of scaffolding tissue within the anterior chamber angle that pulls the peripheral iris up to or anterior to the trabecular meshwork. Treatment primarily consists of aqueous suppressants to decrease inflow. Miotics are of limited benefit because of the obstructed trabecular meshwork. Eyes with extensive PAS often require filtering surgery.

Neovascularization of the Angle

Angle neovascularization generally presents with fine vessels bridging the angle from the peripheral iris to the base of the trabecular meshwork. Eventually, this fibrovascular tissue will contract and produce extensive PAS and cause a rapid rise in the IOP. Treatment is directed to the basic cause of the neovascularization and often requires surgical control of IOP (see Chapter 21).

Membranes

In iridocorneal endothelial (ICE) syndrome, an endothelial Descemet-like membrane may extend from the cornea down over the anterior chamber angle and onto the surface of the iris (Chapter 22). This will obstruct aqueous outflow through the trabecular meshwork, and in later stages may contract to form characteristic PAS. Posterior polymorphous dystrophy is also associated with an epithelial-like membrane across the trabecular meshwork.

In rare instances, epithelium may grow down from a surgical wound. This epithelial down-growth may cover the trabecular meshwork and produce a rise in IOP similar to that seen with ICE syndrome (Chapter 28).

Aniridia

Aniridia is a rare hereditary ocular disorder typically characterized by iris hypoplasia. There is often a stump of iris that is gradually pulled up to the angle wall by irregular attachments. This eventually covers the scleral spur and posterior trabecular meshwork to interfere with aqueous outflow and causes secondary glaucoma⁹⁷ (Chapter 17). In its early stages, the glaucoma may respond to conventional glaucoma medication, but many cases fail to come under satisfactory control. Various surgical procedures have been attempted with limited success including argon laser trabeculoplasty,⁹⁸ goniotomy,^{99,100} filtering procedures,^{99,101} and aqueous shunts.¹⁰²

Iridoschisis

Iridoschisis is an uncommon, often bilateral, disease where the anterior iris stroma splits meridionally into strands that seem to float in the aqueous and gradually

approach the iridocorneal angle.¹⁰³ It usually involves the inferior angle first, but gradually covers the anterior chamber angle to produce secondary glaucoma in about 50% of the patients.^{104,105} The condition can occur at any age, but it tends to occur in older individuals.

POSTERIOR PUSHING MECHANISMS

These conditions result in the peripheral iris being pushed forward to occlude the angle (Table 16–7). Malignant (ciliary block) glaucoma, suprachoroidal hemorrhage, and tumors of the iris and ciliary body can all produce this effect and are discussed in separate chapters. This can also occur in situations that produce anterior rotation of the ciliary body and choroidal effusion.

Anterior Rotation of the Ciliary Body and Choroidal Effusion

Secondary angle-closure glaucoma without pupillary block due to swelling and anterior rotation of the ciliary body and its processes can be caused by a variety of ocular diseases and may follow certain retinal procedures (Table 16–8). Choroidal effusion can have a similar effect. The IOP can rise rapidly and produce the symptoms and signs of acute congestive glaucoma, including corneal edema and a gonioscopically closed angle.

TABLE 16-7 SECONDARY ANGLE-CLOSURE GLAUCOMA WITHOUT PUPILLARY BLOCK: POSTERIOR PUSHING MECHANISMS

Malignant (ciliary block) glaucoma (Chapter 28)
Suprachoroidal hemorrhage (Chapter 43)
Cysts and tumors of iris and ciliary body (Chapter 29)
Intraocular tumors (malignant melanoma, retinoblastoma) (Chapter 29)
Swelling and anterior rotation of ciliary body
Choroidal effusion

TABLE 16-8 CAUSES OF CHOROIDAL EFFUSION AND ANTERIOR ROTATION OF THE CILIARY BODY

Retinal detachment surgery

Panretinal photocoagulation

Autoimmune deficiency syndrome

Postoperative inflammation

Central retinal vein occlusion

Uveal effusion syndrome

Obstruction of uveal blood flow

Nanophthalmos

Dural arteriovenous fistula

Medications

Medical treatment in most cases consists of cycloplegics and topical corticosteroids to reduce congestion and inflammation. Laser iridotomies do not relieve the pressure because there is no pupillary block. It will only aggravate the inflammation. Topical beta-adrenergic antagonists, alpha-agonists, CAIs, and hyperosmotic agents will reduce the IOP during the acute phase. In most cases the glaucoma will resolve within a week, and the pressure elevation will not be high enough to warrant surgical intervention. If medical therapy fails, then iridoplasty can be considered.

Retinal Detachment Surgery

Acute angle-closure glaucoma can occur after a scleral buckling procedure in 1 to 7% of cases.¹⁰⁶⁻¹⁰⁹ In these cases, the constricting band is thought to indent the eye sufficiently to cause anterior rotation of the ciliary body, although some may develop pupillary block from anterior displacement of the lens.¹¹⁰ Additional causes include inflammation and interference with venous drainage by the encircling band, resulting in congestion and swelling of the ciliary body and choroidal effusion.^{111,112}

Careful examination reveals a shallow anterior chamber, and a closed angle without iris bombé. In some cases, a space is apparent between the lens and the pupillary border.¹¹³ Anterior displacement of the ciliary body, and even a choroidal effusion, may be detected by ultrasonography. Gonioscopy of the contralateral eye shows an open angle.

The entire glaucoma episode may last only 1 to 5 days before the angle opens and the pressure returns to normal. However, in that time irreversible damage to the optic nerve can occur if the IOP is highly elevated.

Panretinal Photocoagulation

Panretinal photocoagulation (PRP) may be followed by shallowing of the anterior chamber and occasionally by an acute pressure elevation.^{114,115} This complication can be avoided by giving fewer than 1000 laser burns in a single session, and using a power less than 1 watt, whenever possible.

Most patients who develop angle-closure glaucoma after PRP are asymptomatic. When angle closure does occur, it may take several days before the anterior chamber spontaneously deepens. Delay in treatment of markedly elevated IOP can result in optic nerve damage.

Acquired Immune Deficiency Syndrome

Acute bilateral angle-closure glaucoma without pupillary block has been described in patients with acquired immune deficiency syndrome (AIDS). Such cases will have a choroidal effusion, a deep anterior chamber, and absence of iris bombé. There is no evidence of pupillary

block, and the patients respond to cycloplegics and topical corticosteroids.¹¹⁶

Nanophthalmos

Nanophthalmos is a rare developmental anomaly that can lead to a devastating form of angle-closure glaucoma. It results from arrest in ocular development after closure of the embryonic fissure. Originally described by Brockhurst¹¹⁷ it occurs in patients who are extremely hyperopic and have a small corneal diameter, small globe, short axial length, shallow anterior chamber, and narrow angle. However, the lens is normal in size, producing a crowded, shallow anterior chamber.

Patients with nanophthalmos have an abnormally thick sclera that can impede venous drainage through the vortex veins¹¹⁸ and causes a high resistance to bulk outflow of the proteinous suprachoroidal fluid.^{119–121} Both of these factors appear to predispose these eyes to uveal effusion, forward lens movement, and further narrowing of an already compromised angle.¹²²

Patients may present with chronic angle closure in the fourth to sixth decades of life. Although patients may have some degree of pupillary block, laser iridotomy often does not control the IOP. Unfortunately, surgical intervention often leads to a massive choroidal effusion, exudative retinal detachment, and acute angle-closure glaucoma.^{117,123,124} A postoperative uveal effusion causes swelling and forward rotation of the ciliary body to produce angle closure, whereas forward movement of the lens–iris diaphragm aggravates the pupillary block. The result is a marked elevation of the IOP. Kimbrough has described two cases in which peripheral choroidal effusion preceded any surgical intervention.¹²² This suggests that choroidal detachment may be the instigating factor in at least some individuals.

Surgical treatment of nanophthalmos can produce serious complications, including choroidal and retinal detachment, delayed reformation of the anterior chamber, malignant glaucoma, and loss of vision. Therefore, medical management and laser iridotomy are preferred whenever possible. However, whenever surgical intervention becomes necessary, a posterior sclerotomy should be performed before entering the eye to lessen the chance of choroidal effusion.¹²⁵ In some cases, a sclerotomy alone has been reported to lower the IOP, eliminating the need to perform a filtering procedure.¹²⁶

Medications

Oral sulfa-based medications can occasionally produce ciliary body edema and anterior rotation along with choroidal effusion, leading to bilateral nonpupillary block angle-closure glaucoma. Laser iridotomies are ineffective and the glaucoma must be managed by discontinuing the offending agent and controlling IOP medically until these effects are resolved, which can take 1 to 2 weeks.^{127,128}

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CHILDHOOD GLAUCOMA

John R. Samples, M.D.

Most forms of glaucoma that present in childhood result from aqueous humor outflow obstruction due to abnormal development of the anterior chamber angle, ocular inflammation, or trauma. (Table 17-1). Primary congenital glaucoma often will present in infancy with photophobia, epiphora, and blepharospasm due to corneal edema from elevated intraocular pressure (IOP). In these young children, corneal enlargement and breaks in Descemet's membrane (Haab's striae) are common, due to stretching of the immature connective tissues. Abnormal insertion of the iris anterior to the scleral spur and frequently on the trabecular meshwork is consistent with the etiology of an arrest in the normal events of anterior chamber angle development from the neural ectoderm. Juvenile glaucoma, presenting in older children and young adults, demonstrates a similar angle appearance, but without enlargement of the cornea and sclera. Both forms of glaucoma have been linked to several specific genetic loci.

Several rare, bilateral conditions, collectively considered the Axenfeld-Rieger syndrome, can present with a prominent Schwalbe's line and iris processes, with or

without associated iris thinning and corectopia. Some cases also develop nonocular anomalies of other structures derived from the neural ectoderm, such as the face and teeth. Peters' anomaly is characterized by a central corneal opacity and iris adhesions, either with or without lens involvement. Although some cases are also associated with the peripheral angle changes of Axenfeld-Rieger syndrome, Peters' anomaly and its associated glaucoma appear to result from several different mechanisms.

Aniridia, characterized by a shortened, but not entirely absent iris, probably results from incomplete iris development. In these patients, glaucoma typically presents in childhood or later, as the iris stump rotates forward and obstructs the trabecular meshwork. This condition has many important ocular and systemic associations, including corneal pannus, macular hypoplasia, Wilms' tumor, and renal abnormalities. Patients with aniridia should be thoroughly evaluated for these conditions.

Medical management is frequently employed to temporize until surgery can be performed. However, it may be the mainstay of therapy in those conditions that are not amenable to surgical management. In most of these conditions, glaucoma management relies heavily on surgical procedures, such as goniotomy and trabeculotomy. Refractory cases may require trabeculectomy with antimetabolites, aqueous shunts, and even cyclodestruction.

TABLE 17-1 CLASSIFICATION OF CHILDHOOD GLAUCOMA

Congenital glaucoma
Juvenile glaucoma
Axenfeld-Rieger syndrome
Peters' anomaly
Aniridia
Inflammation
Trauma
Phakomatoses (Chapter 30, Table 30-5)
Metabolic diseases (Chapter 30, Table 30-6)
Systemic congenital syndromes and chromosomal anomalies (Chapter 30, Tables 30-7 and 30-8)

DEVELOPMENT OF THE ANTERIOR CHAMBER ANGLE

Understanding the development of the trabecular meshwork and cornea helps the clinician understand the etiology of the major types of glaucoma that present in childhood (Table 17-2). By the fifth to sixth week of gestation, the lens vesicle separates from the surface ectoderm, from which it develops as an invagination.¹ At about this same

TABLE 17-2 DEVELOPMENT OF THE ANTERIOR CHAMBER ANGLE

5 to 6 weeks	Undifferentiated cells of neural crest origin mass anterior to the periphery of the lens; will provide portions of the cornea, iris, and anterior chamber angle
6 to 8 weeks	Corneal endothelium, stroma, and iris stroma/pupillary membrane form in three waves
3 to 4 months	Anterior iris aligned with periphery of the corneal endothelium; mesenchymal cells form early trabecular meshwork
5 to 7 months	Trabecular meshwork undergoes progressive differentiation and growth into multiple lamellae; multilayered mesodermal cells/endothelium develop perforations and communicate with anterior chamber
Birth	Iris and ciliary body aligned with scleral spur
1 st year of life	Iris root lies posterior to scleral spur, exposing the ciliary body band and creating the angle recess

time, a mass of undifferentiated cells, derived from the neural crest, forms at the periphery of the lens, just anterior to the edges of the optic cup.² Between the sixth and eighth weeks, the corneal endothelium, the iris stroma, and the corneal stroma are formed as cells from this tissue move anteriorly in three successive waves.³

During this time, the anterior chamber begins to form, initially appearing as a slit. By the third and fourth months of gestation, the anterior chamber angle is formed by the junction of the anterior iris surface with the peripheral corneal endothelium.⁴ By the fifth month, the angle recess lies at the level of Schlemm's canal, and it progressively moves posteriorly for a period of time extending well into the first year of life. At birth, the iris and ciliary body insert at the level of the scleral spur,⁵ but after several months this insertion lies more posterior, creating the angle recess. As seen by gonioscopy, the neonatal angle appears to have a relatively anterior insertion of the iris and ciliary body. In the adult, the angle is more open to the anterior face of the ciliary body, revealing the ciliary body band.

PEARL... At birth, the iris and ciliary body insert at the level of the scleral spur. Over the next several months, this insertion moves more posterior, creating the adult angle recess.

The trabecular meshwork appears to begin developing during the third and fourth months of gestation from a nest of primordial mesenchymal cells located immediately anterior to the anterior chamber angle.⁶ Over the next 2 months, this tissue increases in size and cellularity, differentiating into multiple collagenous lamellae lined by endothelium.

The innermost layer of the developing trabecular meshwork initially presents a smooth appearance to the anterior chamber. Some investigators feel that this is a true endothelial lining,⁷⁻⁹ whereas others have noted that this surface consists of multiple layers of mesenchymal tissue.⁴ Regardless of its nature, this surface disappears by about the seventh month, either by cavitation, retraction, or development of intercellular gaps. This exposes the trabecular meshwork to the anterior chamber.^{3,4,7,9,10} One study suggests that this communication may develop as early as the fifth month.⁶ As the angle recess deepens, all of the open spaces of the meshwork come into direct contact with the anterior chamber.

EXAMINATION TECHNIQUES FOR CHILDHOOD GLAUCOMA

Most ocular examination techniques in children are similar to those described in other sections of this book for adults. However, infants and young children unable to cooperate with these procedures generally require sedation or general anesthesia. The presence of general anesthetics and the need to examine the child in the supine position require specific considerations for performing gonioscopy, tonometry, and ophthalmoscopy.

GONIOSCOPY

Gonioscopy is essential for establishing the proper diagnosis in children with glaucoma. This can be accomplished in older, cooperative children using methods discussed in Chapter 5. In the sedated child, gonioscopy can be performed with a variety of contact goniolenses.

The Koeppe contact lens, in combination with a loupe and hand-held slit beam, offers an undistorted view of the angle contour and appearance. Bilateral examination, with a lens simultaneously on each eye, offers rapid comparison between eyes. Direct examination of the angle through the operating microscope using the Swan or Barkan lens allows a good surgical view of the angle, but requires significant rotation of the globe. Standard, indirect examination of the angle using either a Zeiss or Goldmann lens offers higher magnification. However, the surgeon must be careful not to distort the angle by unnatural compression with the edge of the lens.

TONOMETRY

Accurate tonometry is an essential part of the pediatric ocular examination because the majority of childhood glaucomas are associated with elevated IOP. Because of the presence of corneal abnormalities in many of these patients, the Pneumatonometer (Mentor) may be preferable to the Tono-Pen (Mentor), Kowa (Keeler, Windsor, U.K.), or Perkins (Haag-Streit, Mason, Ohio) hand-held applanon tonometers.¹¹ Many of these issues are discussed

in Chapter 6. Using more than one tonometer can minimize potential errors due to corneal hydration, increased corneal diameter, and altered corneal curvature. The Schiøtz tonometer is not recommended in pediatric patients because of decreased scleral and corneal rigidity in these young eyes.

Crying or straining can compromise the accuracy of pressure measurements taken in the office, often to a surprising degree. This effect can be quite variable, probably due to alterations in how elevated episcleral venous pressure influences outflow. If possible, it is best to wait 5 or 10 minutes after an infant has ceased to cry before measuring the IOP.

As discussed in Chapter 6, general anesthesia can lower IOP. Although studies have suggested that IOP is not compromised by end-tidal halothane concentrations up to 1.0%, IOP readings are affected by tracheal intubation.¹² It is optimal to measure IOP in children receiving up to 1% halothane in 66% nitrous oxide during the first 10 minutes after induction but prior to tracheal intubation. These considerations should always be discussed with the anesthesiologist prior to surgery.

OPHTHALMOSCOPY

Assessment of the optic nerve in patients with childhood glaucoma is critical to determining the course of future treatment. Whenever possible, the examiner should use more than one examination technique. In general, direct ophthalmoscopy provides the most highly magnified view of the optic nerve head and nerve fiber layer. In addition, it is highly versatile and can be used in conjunction with the Koeppe contact lens.¹³ Stereoscopic methods, usually using the operating microscope with the aid of a contact lens, offer the advantage of a three-dimensional view. Topical glycerin may be necessary for acute clearing of corneal edema to improve the view. In some instances, preoperative treatment with aqueous suppressants may produce a clearer cornea and facilitate the examination.

When feasible, ophthalmoscopy should be augmented by optic nerve photography to provide a more objective, permanent record. Although potentially useful for long-term monitoring of the optic nerve head, computerized retinal tomography methods (Chapters 11 and 12) are not yet adapted for examining the supine patient under general anesthesia.

PRIMARY CONGENITAL GLAUCOMA (PRIMARY INFANTILE GLAUCOMA; PRIMARY CONGENITAL OPEN-ANGLE GLAUCOMA)

Congenital, or infantile, glaucoma is typically defined as an open-angle glaucoma, without associated ocular anomalies, that presents from birth to approximately 3

years of age. When glaucoma occurs after age 3, increased IOP does not cause stretching of the sclera and cornea, due to the maturation of the connective tissues. These cases are referred to as juvenile glaucoma, which will be discussed in the subsequent section.

BACKGROUND AND PATHOPHYSIOLOGY

Primary congenital glaucoma generally occurs within the first 2 years of life, although the vast majority of cases present by age 1. Its incidence is estimated at 1 in 10,000 births, and males are more affected than females. Most cases are sporadic, although approximately 10% are familial.

Pathological analysis of eyes with congenital glaucoma reveals features consistent with an arrest in the normal events of angle development. These include an anterior placement of the iris root and ciliary body, often anterior to the scleral spur, partially or completely covering the trabecular meshwork.¹⁴ In addition, the trabecular meshwork is compressed and poorly developed.^{4,15,16}

Barkan proposed that a membrane resulting from incomplete resorption of the mesodermal lining of the anterior chamber angle covers the trabecular meshwork and causes elevated IOP in congenital glaucoma.¹⁷ However, such a membrane has not been demonstrated histopathologically.⁴ Because of the significant morphological abnormalities already noted, incomplete development and differentiation of the outflow tissues is the most likely cause of aqueous outflow obstruction in congenital glaucoma. In addition, some investigators have suggested that the anterior insertion of the ciliary muscle may produce compression of the trabecular meshwork and Schlemm's canal.¹⁸

Genetic studies have linked two loci with congenital glaucoma, one on the first and the other on the second chromosome. One of these has been associated with the cytochrome P450 gene, which is hypothesized to contribute to normal angle development (Chapter 2).^{19,20}

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Congenital glaucoma classically presents with photophobia, blepharospasm, and epiphora (Fig. 17-1A). All of these are likely secondary to corneal edema that results from the effect of elevated IOP on the corneal endothelium. Corneal edema can also result from breaks in Descemet's membrane due to enlargement and stretching of the corneal stroma (Fig. 17-1B). These changes are more commonly seen in advanced cases.

Enlargement of the globe (buphtalmos) is generally apparent as an enlarged cornea. This is most easily detected in unilateral or asymmetric cases. Measurement of the horizontal corneal diameter provides an objective record and is an important part of the examination. Children under 1 year of age with a horizontal corneal diameter over 12 mm should be evaluated for congenital

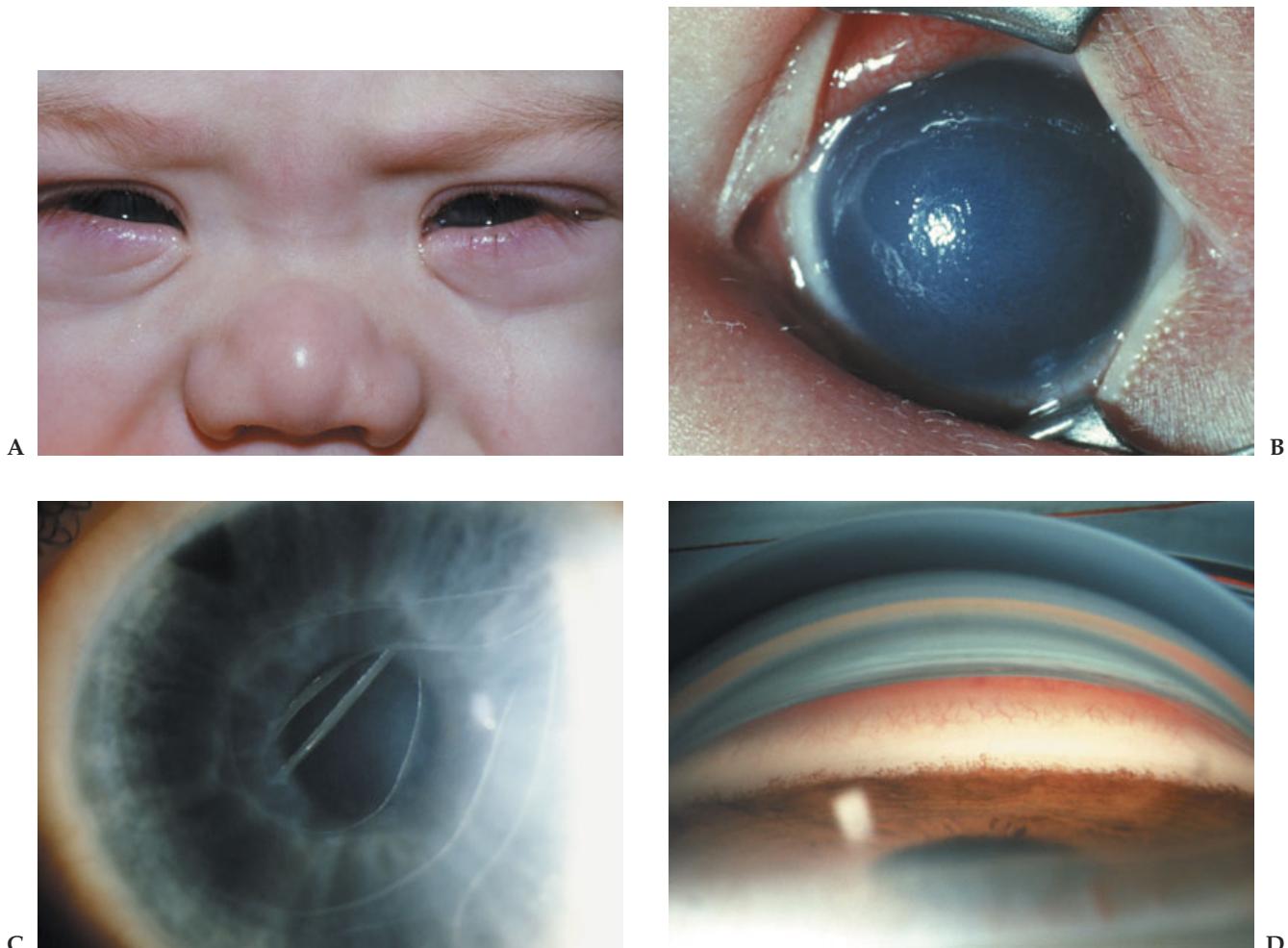


FIGURE 17-1 Congenital glaucoma. (A) Photophobia, blepharospasm, and epiphora constitute a typical presentation. (B) Corneal edema and enlargement due to elevated pressure. (C) Haab's striae resulting from breaks in Descemet's membrane. (D) Gonioscopy often reveals a flat peripheral iris with a "high" insertion, anterior to scleral spur.

glaucoma because the average corneal diameter at birth is normally 10.5 mm.²¹ Breaks in Descemet's membrane are clinically evident as Haab's striae. These are linear, refractive opacities of the posterior cornea that protrude slightly into the anterior chamber and typically have a concentric or horizontal orientation (Fig. 17-1C). These striae generally persist throughout life, even once the IOP has been normalized and the associated edema clears. Globe enlargement also produces axial elongation and myopia. These changes must be recognized early and managed appropriately to prevent or minimize the development of amblyopia. One way to monitor the infant with congenital glaucoma is to look for an increase in the axial length by ultrasound.²²

Gonoscopically, the normal newborn anterior chamber angle has an iris insertion that is at or just posterior to the scleral spur. The peripheral iris is relatively flat because the normal adult angle recess develops during

the first year of life. The trabecular meshwork itself has a smooth translucent appearance.

In congenital glaucoma, the angle approach is deep, with a normal-appearing but generally flat iris, which in some cases appears to sweep forward to its insertion. Although the angle is open, the iris often inserts anterior to the scleral spur, onto the posterior or midtrabecular meshwork in a variable pattern (Fig. 17-1D). The trabecular meshwork itself may appear thickened, occasionally with an overlying glistening tissue.

IOP in the normal infant is generally felt to be slightly lower than in adults. IOP measurements are sometimes difficult to interpret, due to corneal irregularities, anesthetic effects, or struggling if the child is awake, and pressure readings on more than one occasion are often necessary. In general, though, readings above 20 mm Hg should be regarded as suspicious, particularly if obtained with the child under anesthesia.²³

PEARL... A pressure measurement above 20 mm Hg in an infant should be regarded as suspicious, particularly if obtained under anesthesia.

The normal newborn optic nerve head typically has a small cup, usually less than or equal to 0.2 cup-to-disc ratio. In congenital glaucoma, optic nerve heads will typically have variable amounts of increased cupping. Although cupping is often concentric, preferential damage of the superior and inferior poles of the optic nerve head can occur, similar to that seen in adults.²⁴ Asymmetry of cupping and a cup-to-disc ratio greater than 0.3 should alert the clinician to the possibility of congenital glaucoma. Once the IOP is normalized, optic nerve head cupping is more likely to reverse than in adult glaucoma.²⁵

The differential diagnosis of congenital glaucoma includes conditions that mimic the prominent external abnormalities of this condition. These include epiphora, corneal enlargement, opacification, and tears in Descemet's membrane. They are listed in Table 17-3, along with their major differentiating features. Childhood glaucomas associated with several systemic congenital anomalies and genetic conditions are discussed in Chapter 30. Axenfeld-Rieger syndrome, Peters' anomaly, and aniridia, all discussed later in this chapter, must also be considered.

TABLE 17-3 DIFFERENTIAL DIAGNOSIS OF PRIMARY CONGENITAL GLAUCOMA

Condition	Differentiating Features
<i>Tearing</i>	
Nasolacrimal duct obstruction	Purulent discharge
<i>Corneal enlargement</i>	
Megalocornea	Lack of elevated IOP and optic nerve damage
High myopia	
<i>Corneal opacification</i>	
Sclerocornea	Lack of elevated IOP and optic nerve damage
Posterior polymorphous dystrophy	
Congenital hereditary endothelial dystrophy	
Metabolic abnormalities	
<i>Tears in Descemet's membrane</i>	
Birth (forceps) trauma	Vertical orientation of breaks
Axenfeld-Rieger syndrome	Peripheral angle anomalies Iris changes
Peters' anomaly	Central corneal opacity

IOP, intraocular pressure.

MANAGEMENT

The management of congenital glaucoma is primarily surgical. Medical management is mostly used to control IOP in preparation for surgery. In addition to protecting the optic nerve in eyes with particularly high IOP, medical management will often help reduce corneal edema. This facilitates the examination of the anterior chamber and angle and the optic nerve head, and improves the likelihood of a successful surgery, if the surgeon chooses to perform a goniotomy. Surgery for congenital glaucoma consists of opening the trabecular structures into Schlemm's canal, with either a goniotomy or a trabeculotomy. These procedures and their relative strengths and weaknesses are described in a subsequent section.

In general, goniotomy and trabeculotomy appear to be equally successful in treating congenital glaucoma, and the choice of procedure should be that with which the surgeon is most familiar.²⁶ Success rates appear to vary widely, depending on the severity of glaucoma at diagnosis and the age at diagnosis. Surgery performed between 2 months and 2 years of age appears to have the greatest chance of success, with success rates of over 90% for both goniotomy and trabeculotomy using one or more procedures.^{27,28} Success of surgery in younger or older children is significantly reduced.

JUVENILE GLAUCOMA

Juvenile glaucoma is a rare condition with an onset between 10 and 35 years and a higher incidence among persons of African heritage.^{29–31} It is similar to adult primary open-angle glaucoma because the anterior chamber angle is open and the trabecular meshwork is normal in appearance.

Linkage analysis has found a defective gene on the long arm of chromosome 1 associated with this disorder in some, but not all, patients, and specific mutations may correlate with severity. This has been associated with mutations in the *TIGR/MYOC* gene, and many of these patients have markedly elevated IOP with poor response to medical therapy.^{32,33} These patients seem to do best with early recognition and surgical control of IOP.

AXENFELD-RIEGER SYNDROME

This is an unusual group of bilateral congenital anomalies that are the product of abnormal development of the anterior chamber angle, the iris, and the trabecular meshwork. Many cases are associated with glaucoma and are also sometimes associated with other ocular and systemic abnormalities.

BACKGROUND

The first of these conditions was recognized by Axenfeld, who described a patient with a prominent, anteriorly

displaced Schwalbe's ring with multiple, attached iris processes.³⁴ Rieger later observed that some of these patients also had iris hypoplasia and altered pupils (Rieger's anomaly).³⁵ Still other patients were found to have other ocular and systemic developmental defects involving the teeth and facial bones (Rieger's syndrome).³⁶

Over the years, the terms *mesodermal dysgenesis syndrome* and *anterior cleavage syndrome* also have been used to describe these conditions.^{37,38} However, neither is accurate because the angle structures probably originate from ectodermally derived neural crest cells rather than from mesoderm, and current concepts of angle development do not include a cleavage process.³⁹ Because these disorders appear to result from abnormal development from cells of neural crest origin, the term *neurocristopathies* has been suggested by some.² Other terms, such as *trabeculodysgenesis*, *iridodysgenesis*, and *corneodysgenesis* have been proposed on the basis of the structures involved.⁴⁰ However, this concept may result in the grouping of disorders that actually have a variety of biochemical origins and associations unrelated to these particular conditions.

There is a close relationship between Axenfeld's anomaly, Rieger's anomaly, and Rieger's syndrome, and patients often will have one or more features of these conditions. Because of this, these disorders are best considered as a clinical spectrum called Axenfeld-Rieger syndrome, as suggested by Shields.^{41,42} In the past, some authors have included Peters' anomaly with these conditions. However, the defect in Peters' anomaly appears to occur later in embryological development and involves different mechanisms. This entity will be discussed in the subsequent section.

These disorders are usually bilateral with autosomal dominant inheritance. Glaucoma occurs in about half of the patients. The other ocular and systemic abnormalities are variable in the frequency and severity of their occurrence. In many cases the glaucoma and ocular and systemic abnormalities may not be recognized until later in childhood.

PATHOPHYSIOLOGY

Shields has suggested that the Axenfeld-Rieger syndrome probably results from an arrest in the normal development of the anterior chamber angle from the neural crest.⁴² In this theory, the smooth surface lining of the fetal anterior chamber, possibly endothelium, persists in the anterior chamber angle and on the surface of the iris. This produces the iris processes, whereas contraction of the retained cells causes the corectopia and iris stromal defects that are seen in the Rieger's variant. Abnormal development of other tissues derived from the neural crest may affect the development of structures such as the face and teeth, leading to abnormalities of Rieger's syndrome.

Genetic analyses have demonstrated an association of Axenfeld-Rieger syndrome with several loci, the genes of which appear to be important to angle development.⁴³⁻⁴⁶ These considerations are more fully discussed in Chapter 2.

In cases associated with glaucoma, the arrested angle development appears also to lead to features typical of congenital glaucoma, including a poorly developed trabecular meshwork and an anterior insertion of the iris root. Several reports have documented significant structural alterations in the trabecular meshwork and Schlemm's canal.^{41,42,47} These include thickened and compacted trabecular beams with an incomplete endothelial covering. These changes may also be accompanied by insertion of the peripheral iris and ciliary body into the trabecular meshwork. A normal Schlemm's canal is often absent.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Axenfeld's Anomaly and Syndrome

In 1920, Axenfeld described an anomaly in a patient's cornea that had a white ring that was contiguous with the limbus and he called it posterior embryotoxon.³⁴ This appearance was due to a prominent, anteriorly displaced Schwalbe's ring to which multiple peripheral iris strands were adherent (Fig. 17-2A,B).

Schwalbe's line, located along the anterior border of the trabecular meshwork, is thickened or hypertrophic and displaced anteriorly enough to be seen clinically as a visible membranous line behind clear cornea. Unlike arcus senilis there is no lucid interval between the ring and the limbus. On gonioscopy, Schwalbe's line appears to actually protrude into the anterior chamber as a ring.⁴⁸ This ring need not extend for a full 360 degrees.

The iris processes may be broad or relatively fine and vary in number from a few to many. They may be separated from the cornea by a fine membrane and may break free of the cornea, leaving portions hanging in the anterior chamber.⁴⁹ The actual iris insertion is usually anterior in these cases and often obscures the scleral spur. Axenfeld's anomaly may occur alone or in association with glaucoma, in which case it is called Axenfeld's syndrome.⁵⁰

Posterior embryotoxon alone occurs in 10 to 15% of normal eyes (Fig. 17-2C).⁵¹ It is usually temporal and does not increase the risk for glaucoma. Although autosomal dominant transmission has been described, isolated posterior embryotoxon is often likely to be an anatomic variation. A prominent Schwalbe's line may be associated with disorders other than primary congenital glaucoma.⁵²

Rieger's Anomaly

In 1935, Rieger described a condition with posterior embryotoxon and iris adhesions plus hypoplasia of the iris and corectopia, which he termed mesodermal dysgenesis of the cornea and iris.³⁵ The iris may be thin with

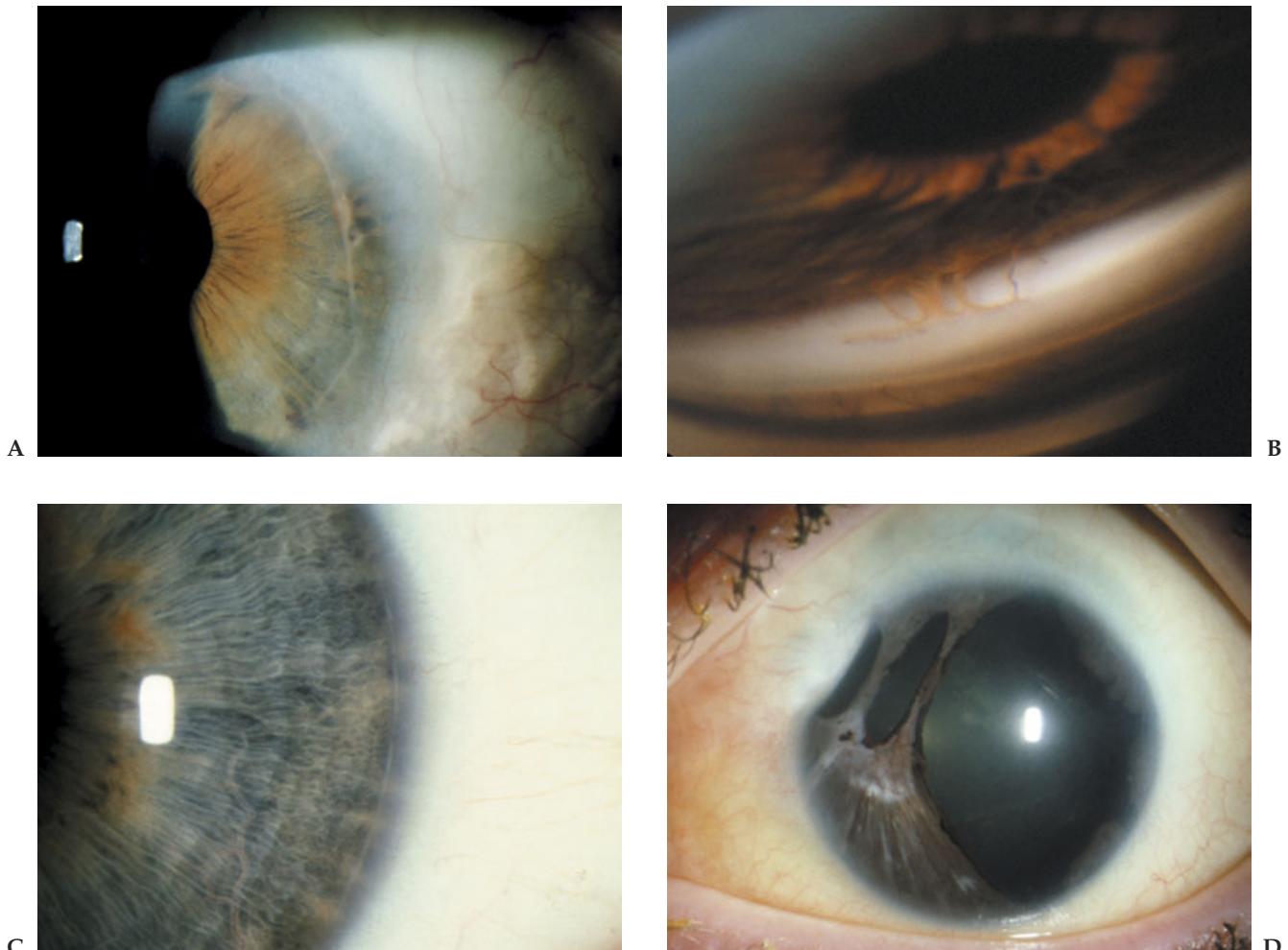


FIGURE 17-2 Axenfeld-Rieger syndrome. (A) Prominent anteriorly placed Schwalbe's line in a patient with Axenfeld's syndrome. (B) Iris processes extending to Schwalbe's line. (C) Temporal, isolated posterior embryotoxon in an otherwise normal eye. (D) Rieger's anomaly in a patient with glaucoma. Note corectopia and iris atrophy in opposite quadrant that has progressed to a large hole.

areas of atrophy and hole formation, leading to both corectopia and polycoria (Fig. 17-2D). Occasionally, the iris changes are progressive,⁵³ and there may be associated glaucoma. A variety of systemic associations have been described, producing Rieger's syndrome.⁵⁴

Rieger's Syndrome

Some patients with Rieger's anomaly may also have developmental defects of the teeth and facial bone, including microdontia and hypodontia.³⁶ Other defects include redundant periumbilical skin, hypospadias, and maxillary hypoplasia. Several patients with Rieger's syndrome have also been shown to have empty sella syndrome.⁵⁵

Glaucoma in Axenfeld-Rieger Syndrome

Glaucoma occurs in about half of the patients with Axenfeld-Rieger syndrome, due to abnormal development of the trabecular meshwork and Schlemm's canal. It is not

always seen during infancy and may not become evident until late childhood. Interestingly, the presence and the severity of the glaucoma do not correlate well with the extent of iris adhesions and defects. Often the angle is open behind the adhesions.

Differential Diagnosis

Several conditions can be confused with the Axenfeld-Rieger syndrome, usually due to similarities in the abnormalities of the iris, cornea, and anterior chamber. These are listed in Table 17-4, along with major differentiating features.

MANAGEMENT

Management of glaucoma in patients with Axenfeld-Rieger syndrome is difficult. Medications, particularly aqueous humor suppressants, may be effective, although many patients will require surgery. Goniotomy has been

TABLE 17-4 DIFFERENTIAL DIAGNOSIS OF AXENFELD-RIEGER SYNDROME

Condition	Differentiating Features
Iridocorneal endothelial syndrome	Unilateral Middle age Corneal endothelial abnormalities
Isolated posterior embryotoxon	Lack of glaucoma, iris changes
Aniridia	Iris hypoplasia Associated corneal and macula changes
Iridoschisis	Lack of angle abnormalities, glaucoma
Peters' anomaly	Corneal changes
Ectopia lentis et pupillae	Lack of glaucoma
Oculodental digital dysplasia	Lack of angle changes, glaucoma

reported to be effective in some younger patients,⁵⁶ but this procedure can be complicated by the extensive iris process and should probably be avoided in patients with large areas of contact between the iris and cornea. Trabeculotomy, too, has a high risk for substantial bleeding, endothelial cell damage, and inflammation in eyes with thick corneal-iris adhesions. Some authors have concluded that filtering surgery with antimetabolites is the best surgical procedure for these patients.⁵⁷ Eyes that fail trabeculectomy may require an aqueous shunt, or, ultimately, diode cyclophotocoagulation (CPC).

PETERS' ANOMALY

Peters' anomaly is a bilateral condition in which there is a central corneal opacity with adhesions between the central iris and posterior cornea (Fig. 17-3A,B). The

anomaly can be regarded as Type I or Type II, depending upon whether the lens is normal (Type I) or abnormal (Type II). The condition is usually sporadic, although autosomal recessive and autosomal dominant transmission both have been reported.⁵⁸ Approximately 50% of patients will have associated glaucoma. Some cases can have the peripheral anterior chamber angle abnormalities of Axenfeld-Rieger syndrome, which may lead to diagnostic confusion.

BACKGROUND AND PATHOPHYSIOLOGY

Von Hippel first reported the appearance of patients with a central corneal opacity, iris adhesions, and glaucoma.⁵⁹ He attributed this to an intrauterine corneal infection and perforation, leading to the iris or lens adhesions (von Hippel's internal corneal ulcer). Peters later suggested that these abnormalities resulted from incomplete development and faulty separation of the lens from the lens vesicle and from the surface ectoderm.⁶⁰ More recent work suggests that, in some cases, the defect results from abnormal migration of the neural crest cells to form the anterior segment.⁶¹ However, multiple mechanisms probably contribute. Over the years, several terms have been used for Peters' anomaly. These include *posterior keratoconus*, *anterior chamber cleavage syndrome*, and *primary dysgenesis of the cornea*, many of them leaning on older concepts of anterior chamber development.

PITFALL... Although some patients with Peters' anomaly demonstrate anterior chamber angle abnormalities of Axenfeld-Rieger syndrome, Peters' may result from several mechanisms and these are probably distinct entities.

The etiology of Peters' anomaly Type I is likely related to embryologic arrest. The annular corneal opacity corre-



A

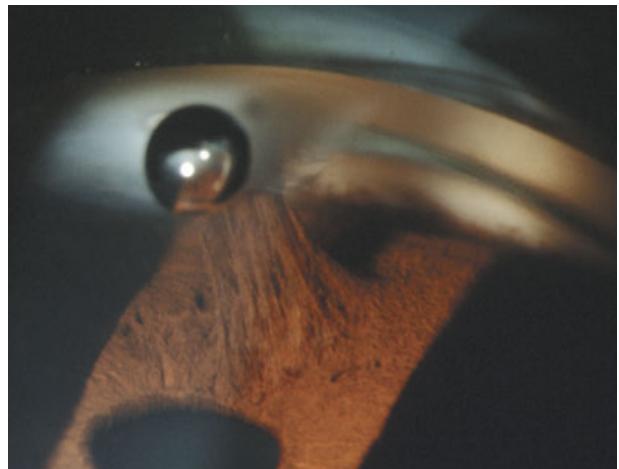


FIGURE 17-3 Peters' anomaly. (A) Circumscribed central corneal opacity. (B) Gonioscopy of fellow eye demonstrates iris process in foreground leading to the opacity.

B

sponds to a central defect in the corneal endothelium and underlying Descemet's membrane, in many cases due to incomplete migration of the neural crest-derived mesenchymal cells. Patients with Peters' anomaly may also have defects in the posterior stroma, Descemet's membrane, and endothelium, with or without extension of iris tissue strands from the iris collarette to the edge of the corneal leukoma.

It is not likely that the lens has the role proposed by Peters because it is often clear. The concurrent presence of a normal trabecular meshwork and adjacent structures in these cases also argues against a complete arrest in early development. The lesion is likely to occur after full differentiation of the anterior segment (10 weeks) and before Descemet's membrane is well formed (16 weeks).

Cases with lens involvement (Peters' Type II) have been reported to show stalklike connections between the lens and posterior cornea, or apposition of an otherwise intact lens capsule to the posterior corneal layers.^{62–64} This latter finding suggests that the lens formed normally and later moved into apposition with the cornea. Several mechanisms for such secondary anterior movement of the lens have been proposed, including anoxia, pupillary block, and pressure from posterior masses. The wide range of abnormalities seen with this condition suggests that multiple different mechanisms are likely responsible for Peters' anomaly.

Glaucoma may, in some cases, result from incomplete differentiation of the trabecular meshwork, with peripheral angle changes similar to those described for Axenfeld-Rieger anomaly. In one patient with Peters' anomaly and peripheral anterior synechiae, Schlemm's canal and trabecular meshwork could not be identified.⁶⁵ In most cases, however, the mechanism of aqueous outflow obstruction is not clear.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In Type I Peters' anomaly there is an annular opacity in the central visual axis with iris strands that extend across the anterior chamber to the opacity. The iris strands often originate from the iris collarette. The lens is usually clear and the defect may be one primarily related to corneal endothelial development.⁶³ Other associations include microcornea and an angle that retains the characteristic appearance of primary congenital glaucoma on gonioscopy. Early cases demonstrate fine corneal haze, due to associated corneal edema, which fades in time to reveal the more distinctive corneal scar.

Peters' anomaly Type II is characterized by lens abnormalities in addition to the central corneal opacity, which is generally more dense than in Peters' Type I. In some instances, the lens lies in juxtaposition to the corneal surface. In others, the lens is in normal position and its surface appears intact but a cataract is present. Glaucoma occurs in approximately half of the patients

with Peters' anomaly. Here, too, the angle generally appears normal, although some cases may be associated with anterior chamber abnormalities similar to Axenfeld-Rieger syndrome.

Peters' anomaly may occur in association with systemic abnormalities involving a wide range of organ systems including the heart, genitourinary system, musculoskeletal system, congenital ear anomalies, hearing loss, cleft palate, and spinal defects.⁶⁶ Some work suggests that patients with corneolenticular adhesions are more likely to have systemic and other ocular anomalies.⁶⁷

The differential diagnosis of Peters' anomaly includes several causes of corneal opacities that may be seen in children. These include sclerocornea, where the entire cornea is opacified with the central cornea being modestly clear and usually flattened.⁶⁸ Iridocorneal adhesions and poor development of angle structures may also occur with sclerocornea, which may be difficult to detect gonioscopically due to the opaque cornea.^{69–71} Aniridia, described in the following text, may also create confusion, particularly when more than a rudimentary stump of iris remains. Trauma associated with forceps delivery during birth, as well as congenital glaucoma can also lead to opacities of the central cornea, as can mucopolysaccaridoses and congenital hereditary corneal dystrophy (CHED) and a perforated corneal ulcer.

MANAGEMENT OF PETERS' ANOMALY

Management of Peters' anomaly primarily relies on controlling glaucoma, when present, and preventing amblyopia. Detection of glaucoma is complicated by the corneal opacity, which affects the accuracy of tonometry and obscures the clinician's view of the anterior chamber angle and optic nerve head. Controlling IOP is generally similar to methods described for Axenfeld-Rieger syndrome. Although some cases may respond to medical management, many cases ultimately may require filtering surgery. Penetrating keratoplasty represents the best chance of preventing amblyopia in eyes with dense and large central corneal opacities. However, successful outcomes in this young age group are not common, particularly when a cataract or other anterior segment abnormalities are present.^{72,73}

ANIRIDIA

Aniridia is a rare, bilateral, developmental disorder that occurs in about 1.8 per 100,000 births.⁷⁴ It is characterized by marked iris hypoplasia and, sometimes, nearly complete absence of the iris (Fig. 17–4). Despite the name, there is always a rudimentary stump of iris in the anterior chamber angle that is visible by gonioscopy. Aniridia may be associated with multiple ocular and systemic abnormalities including glaucoma, foveal hypoplasia,



FIGURE 17-4 Aniridia, with rudimentary iris and corneal opacity and pannus.

nystagmus, corneal pannus, photophobia, reduced visual acuity, Wilms' tumor, genitourinary problems, and mental retardation.

BACKGROUND AND PATHOGENESIS

Aniridia was initially described in the early 19th century.⁷⁵ Associations of the ocular syndrome with Wilms' tumor and other systemic problems were made in the latter half of the 20th century.⁷⁶

Most cases are familial and are transmitted as an autosomal dominant form. However, about one third of cases are isolated sporadic mutations.⁷⁷ Approximately 20% of sporadic cases are associated with Wilms' tumor.⁷⁸ The aniridia gene locus for both the familial and the sporadic forms is a mutation of the PAX6 gene on the 11p3 chromosome.⁷⁹

Three genetic types of aniridia have been described:⁷⁴ (1) An isolated, autosomal dominant aniridia that is not associated with other systemic manifestations accounts for approximately 85% of all cases. (2) An autosomal dominant aniridia is associated with Wilms' tumor and genitourinary anomalies in about 13% of cases. Mental retardation also occurs and this is sometimes referred to as the WAGR syndrome (Wilms' tumor, aniridia, genitourinary anomalies, and retardation). (3) An autosomal recessive aniridia, associated with cerebellar ataxia and mental retardation, is seen in a small percentage of patients.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The most common symptoms of aniridia are decreased visual acuity, photophobia, nystagmus, and strabismus. These appear to result from the several associated ocular abnormalities that affect the iris, cornea, lens, and fovea.

Iris Abnormalities

Even though the iris may not be seen on gross examination, there is always a rudimentary stump that can be seen by gonioscopy. However, the iris appearance varies greatly, ranging from the rudimentary stump to a complete or nearly complete, although thin, iris. Fluorescein angiography of the iris may demonstrate vascular abnormalities.⁸⁰ At birth, the angle is usually open, the iris does not cover the trabecular meshwork, and there is no glaucoma. However, occasional fine blood vessels extend from the iris root to the trabecular meshwork, or higher. Gradual contraction of these vascular and tissue strands between the peripheral iris and angle wall may be responsible for the eventual closure of the meshwork by the stump of iris.⁸¹

Glaucoma

Ultimately, 50 to 75% of patients with aniridia will develop glaucoma.⁸² Although occasionally associated with congenital glaucoma, glaucoma in aniridia usually develops as the rudimentary stump of iris rotates anteriorly to progressively cover and obstruct the trabecular meshwork. This can be a gradual process, and glaucoma may not occur until the first or second decades of life.⁸¹

Corneal Abnormalities

A peripheral corneal opacity may begin in early life and later extend over the cornea as a cellular infiltrate between the epithelium and Bowman's layer. Subsequently a vascular pannus may extend into the central cornea with complete opacification. Microcornea has also been reported to occur with aniridia.⁸³

Lenticular Defects

Cataracts may be present at birth or, more often, develop later in life, with an incidence of 50 to 85%.⁸⁴ Dislocation of the lens may also occur, due to segmental absence of zonules.

Foveal Hypoplasia

Most patients with aniridia have hypoplasia of the fovea, and this can be identified by the occasional small vessel(s) seen to enter the foveal avascular zone. Fluorescein angiography can help to demonstrate this abnormality.⁸⁰ This hypoplasia of the fovea and macula is responsible for pendular nystagmus and reduced vision.

The differential diagnosis of aniridia includes many of the conditions that can produce angle closure and apparent iris hypoplasia, including end-stage neovascular glaucoma. Corneal opacification from end-stage glaucoma may also be difficult to distinguish from the corneal abnormalities seen in aniridia.

SPECIAL CONSIDERATION

Because of the important systemic associations of aniridia, patients with this finding should have a careful workup, including a detailed family history, ocular and systemic examination, and DNA analysis.

MANAGEMENT

Because of the important systemic implications of aniridia, patients with this diagnosis should have a thorough workup, as outlined in Table 17-5. Management of symptomatic problems primarily revolves around meeting the visual needs of the patient and controlling the glaucoma.

Photophobia is treated with tinted glasses or iris contact lenses, and refractive errors must be corrected. Binocularity should be achieved when macular hypoplasia is not severe and strabismus surgery is therefore indicated at an early age.

Walton has suggested that patients with aniridia should have preventive goniotomy to break any abnormal attachment between the iris stub and the angle wall and to push back iris that might be near or against the trabecular meshwork. Fifty-five eyes were followed for an average of over 9 years, and 89% of these had IOPs less than 22 mm Hg without medications.⁸⁵ However, many such patients can be well managed by medical therapy alone, and this should always be tried first.

Trabeculectomy is often attempted when medical treatment fails to control the IOP, although it will usually fail because there is no iris to protect the lens and there is frequent loss of vitreous.⁸⁶ In general, surgical prognosis in aniridia is reduced in eyes with greater problems from iris abnormalities, corneal opacity, and cataracts. CPC with the contact diode laser has been used to successfully control the IOP, but repeated treatments may be necessary.

TABLE 17-5 ANIRIDIA WORKUP

Family history: ocular abnormality, dental anomaly, protruding umbilicus, genitourinary problems, Wilms' tumor, or mental retardation

Systemic examination: teeth, umbilicus, genitalia, urinary system including renal ultrasound for patients with sporadic aniridia and central nervous system problems, DNA analysis

Ocular examination: thorough ocular examination of the patient, both parents and other relatives, including anterior and/or posterior segment fluorescein angiography of iris and/or macula when needed to help make the diagnosis.

OTHER CAUSES OF CHILDHOOD GLAUCOMA

A wide range of other conditions can be associated with glaucoma during childhood. These include inflammation (Chapter 26) and trauma (Chapter 24). Other conditions, associated with other systemic manifestations, include the phakomatoses, metabolic diseases, and systemic congenital syndromes and chromosomal anomalies. These are discussed in Chapter 30.

MANAGEMENT OF CHILDHOOD GLAUCOMA

MEDICAL MANAGEMENT

Medical therapy for most childhood glaucoma is useful when the IOP is particularly high and temporizing measures are needed. In general, these consist of topical aqueous humor suppressants, all of which are discussed in Section V. Specific considerations particular to treating children are discussed here.

Most clinicians will begin treatment with a beta-adrenergic antagonist, due to our long experience with these drugs and their efficacy and safety. However, parents should always be cautioned about the potential pulmonary side effects. Infants and young children should be treated with cardioselective beta-blockers.

Topical carbonic anhydrase inhibitors are also useful in children, and have an excellent safety profile. Although oral carbonic anhydrase inhibitors can also be used with these disorders, they can produce a rapid and severe acidosis in infants. Oral agents should not be used in children without first consulting their pediatrician.

Pilocarpine is generally less likely to be effective in these disorders because it relies upon a functioning trabecular meshwork. In some cases miotics can produce elevation of IOP, presumably by encouraging further compression of the trabecular meshwork.

Current experience suggests that pediatric glaucomas do not often respond well to prostaglandin analogs, although selected cases may demonstrate an impressive response.^{87,88} This is not surprising, considering the altered anterior chamber angle anatomy of many of these conditions. Chronic use of these agents should be carefully considered, particularly considering their potential long-term ocular side effects.

Iopidine and brimonidine appear to have similar efficacy in lowering IOP in children, although brimonidine may produce fewer allergies and have less tachyphylaxis. Brimonidine should never be used in very young children due to the risk of severe central nervous system depression.⁸⁹⁻⁹¹ Because of these concerns, brimonidine should also not be used in neurologically impaired children.

SURGICAL MANAGEMENT

Goniotomy

Goniotomy, which uses a fine-needle knife to incise the anterior meshwork, was initially described by Barkan.⁹² As originally described, he felt this procedure opened a membrane overlying the meshwork. Although this membrane has never been identified histologically, the procedure appears to work by exposing Schlemm's canal, or at least by encouraging posterior movement of uveal tissues that appear to have failed to correctly migrate posteriorly during development.

Performing a goniotomy involves rotating the eye nasally, allowing the surgeon to visualize the nasal 120 degrees of the angle with the aid of an operating gonioprism. This requires the aid of an experienced assistant, who grasps the limbus with locking forceps at the superior and inferior limbus. Once the surgeon has an optimal view, with proper positioning, the knife is inserted into the peripheral temporal cornea and passed across the anterior chamber. Although the original Barkan knife had a shoulder, later revisions incorporate a straight or tapered shaft, ending with a sword point. The nontapered shaft offers the advantage of not allowing aqueous to escape around the knife, which helps keep the anterior chamber formed. Some surgeons use a 23- or 25-gauge needle.⁹³ The prism is then placed on the eye and, under direct visualization, the knife tip is used to incise the tissue lying over the site of Schlemm's canal, using Schwalbe's line as a landmark.

Generally, a successful procedure will produce a white incision line, indicating the posterior movement of tissue from the overlying Schlemm's canal and sclera (Fig. 17-5). After the knife is withdrawn, blood reflux is common and is considered a favorable sign. The anterior

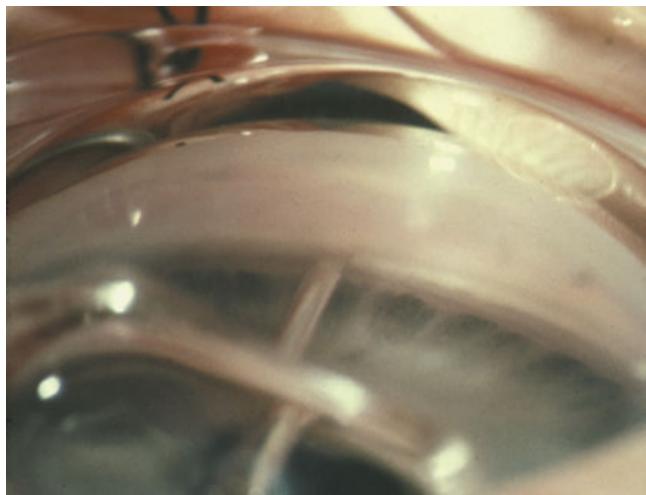


FIGURE 17-5 Goniotomy. Note white incision line following the goniotomy knife, indicating separation of tissues over Schlemm's canal and posterior recession of angle tissues.

chamber is then reformed, either with air or with saline and the incision closed with a fine absorbable suture. If bleeding or flattening of the anterior chamber interferes with the view, the needle should be withdrawn and the anterior chamber deepened.

Typically, 3 or 4 clock hours can be incised in a single procedure, leaving the other quadrant of the nasal angle available for future treatment. Incision of the temporal angle is technically more difficult because this requires that the knife be brought over the patient's nose. Although a second goniotomy may be effective after the initial attempt fails, continued poor control generally will not respond to further such surgery, and the surgeon should consider trabeculotomy to gain access to the temporal angle, or a trabeculectomy.

Postoperative management includes the use of topical antibiotics and frequent topical steroids. Many surgeons will use pilocarpine 2% twice daily to help keep the angle open.

The major advantages of this procedure are its simplicity and the fact that conjunctiva is left undisturbed, in case future filtering surgery is needed. The major disadvantages are the need for exact placement of the incision and the need for an excellent view of the anterior chamber angle landmarks. This may not be possible in children with corneal edema from uncontrolled IOP. Although mechanical removal of the corneal epithelium may improve the view, the angle in some cases will still be obscured by persistent stromal edema, as well as Haab's striae. Complications of goniotomy include accidental trauma to the iris and lens, or accidental incision of the ciliary body or cyclodialysis.

CONTROVERSY

The choice between goniotomy and trabeculotomy depends largely on the surgeon's preference. Whereas the former does not disturb the conjunctiva, the latter can be performed in eyes with cloudy corneas.

Trabeculotomy

Trabeculotomy was initially described in 1960.^{94,95} This involves introducing a rigid metal probe called a trabeculotome into Schlemm's canal via an external approach, usually beneath a trabeculectomy-type flap.

For this technique, a conjunctival flap is made, followed by a partial-thickness flap of limbal sclera, similar to that used for a trabeculectomy. The position of Schlemm's canal viewed through the bed of the scleral flap can be identified by the junction of the clear cornea with the dense white anterior margin of the sclera, which

corresponds to the scleral spur. Making a radial incision across this junction with a sharp knife under high magnification, carefully deepening it with successive passes and spreading the tissues slightly to either side, allows the surgeon to enter the outer wall of Schlemm's canal without entering or perforating the trabecular meshwork. This is usually heralded by the escape of a small quantity of aqueous humor.

The trabeculotome, available in both right and left curves, is then inserted into the canal, keeping the shaft of the instrument parallel to the visual axis to facilitate passage into the canal (Fig. 17-6). The upper arm of the instrument also helps guide this maneuver.

Once the trabeculotome is inserted, the surgeon should first rotate it posteriorly, to be certain that the probe is not in the supraciliary space. If the probe does not rotate, it is probably correctly within Schlemm's canal and it is then rotated anteriorly, through the trabecular meshwork and into the anterior chamber. The procedure is then performed through the opposite side of the meshwork using the other probe. As with goniotomy, a small amount of bleeding is not uncommon. Postoperative treatment includes topical steroids, antibiotics, and pilocarpine.

Trabeculotomy is particularly useful in eyes with significant corneal opacity, although many surgeons will use this for primary surgical treatment. Disadvantages of trabeculotomy include the need to manipulate the conjunctiva, which may interfere with subsequent filtration surgery. Complications include inadvertent cycloidalysis, stripping of Descemet's membrane, and lens damage.

Variations of this basic technique include a combined trabeculectomy with goniotomy. This consists of creating

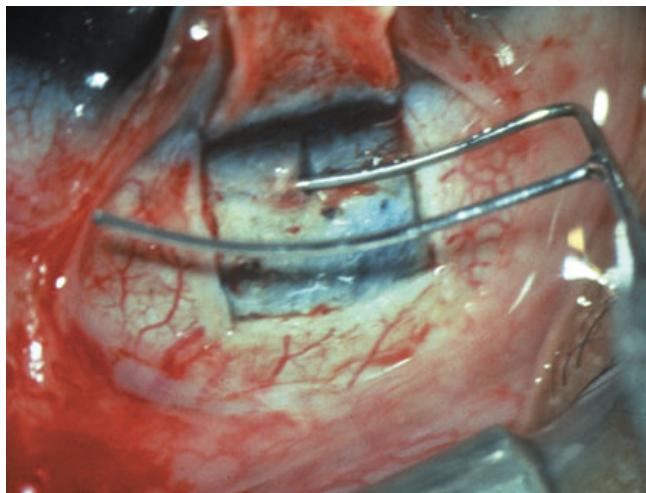


FIGURE 17-6 Trabeculotomy. Trabeculotome is being inserted into Schlemm's canal beneath a trabeculectomy-type scleral flap. Upper arm of trabeculotome helps guide the lower arm along the contour of Schlemm's canal to facilitate insertion.

a trabeculectomy fistula into the anterior chamber following the second pass with the trabeculotome. The scleral flap and conjunctiva are then sutured as for a standard trabeculectomy.⁹⁶ This procedure is particularly useful in cases where the opening to Schlemm's canal is difficult to find or the trabeculotomy is incomplete, or if the mechanism of glaucoma is uncertain.

In another variation, a nylon or blue prolene suture is introduced into Schlemm's canal for several clock hours, using a second trabeculotomy incision to externalize the leading end. Pulling the suture ends straightens the suture, causing it to break through the trabecular meshwork. This technique can be used to create a 360 degree trabeculotomy, often with good results.^{97,98}

Filtration Surgery

Filtration in children with glaucoma is generally reserved for those eyes in which goniotomy or trabeculotomy have failed or are contraindicated, as in some cases of Axenfeld-Rieger syndrome. Although trabeculectomy in young patients has a higher risk of failure, the use of antimetabolites has significantly improved the success rates in this age group. As with the use of antimetabolites in adults, the amount and duration of application are not standardized, and the risk of thin blebs and postoperative infection remains a potential problem.⁹⁹ Chapter 43 provides a complete description of techniques and complications of filtering surgery.

Aqueous Shunts

In cases where a trabeculectomy has failed or is not possible, an aqueous shunt may provide effective IOP control. In general, aqueous shunts in phakic children have a high likelihood of traumatizing the lens. Some surgeons use shunts only in children who are aphakic. Alternatively, the tendency for tubes to rotate anteriorly in children has prompted some to use pars plana tube insertion, combined with a vitrectomy. Techniques and complications of aqueous shunts as well as considerations specific to their use in children are presented in Chapter 45.

Cyclodestruction (see Chapter 42)

Cyclodestruction is generally reserved for glaucoma cases that do not respond either to medications or to surgery designed to improve aqueous humor outflow. Although cyclotherapy was used for many years to treat end-stage pediatric glaucoma, it is no longer recommended because of the high rate of complications, and it has been supplanted by cyclophotocoagulation (CPC).

Transscleral CPC with the contact diode or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser destroys the ciliary epithelium, the ciliary stroma, and its vascular system. This results in reduction of aqueous flow

and lowers the IOP. In CPC, laser energy is generally absorbed by melanin contained within the stromal and epithelial melanophores of the ciliary body. Laser energy is also absorbed by blood, producing substantial thrombosis that can lead to ischemia. This helps create direct destruction of the ciliary epithelium. Both methods have been shown to effectively lower IOP in children with refractory glaucoma, although multiple treatments are often necessary.^{100,101}

Most clinicians prefer filtration with an antimetabolite or a shunt procedure over CPC in eyes where the visual prognosis is generally 20/100 or better. Because cyclodestructive procedures promote inflammation in the eye, it is generally not advisable to use this if a subsequent filtration or implantation of a shunt device is being planned.

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STEROID-INDUCED GLAUCOMA

Abbot F. Clark, Ph.D., and John C. Morrison, M.D.

Although relatively rare, steroid-induced glaucoma presents several connections with primary open-angle glaucoma (POAG). These include a stronger tendency to develop steroid response in the families of patients with POAG, and recent discoveries of tantalizing connections between the glaucoma gene, *MYOC* (*GLC1A*, *TIGR*), and its glucocorticoid induction in the trabecular meshwork (TM). Alterations in TM cell function, morphology, extracellular matrix production, and the cytoskeleton also occur in both of these conditions. These similarities suggest that steroid-induced glaucoma may provide important insights into the genetics and cellular mechanisms of POAG.

Clinically, steroid-induced glaucoma is characterized by highly elevated intraocular pressure (IOP) and is always associated with glucocorticoid administration. The eyes are quiet, and the angle appears normal by gonioscopy. Pressure elevation generally correlates with the steroid dose and is most common with topical and periocular administration, although it can also follow systemic, and even inhaled, steroid use. Because these eyes are generally asymptomatic, diagnosis relies on appropriate recognition and monitoring of patients at risk. Failure to recognize and control elevated pressure can result in characteristic glaucomatous optic nerve damage and irreversible visual field loss.

This glaucoma is best treated by withdrawal of the steroid preparation, and standard topical glaucoma management, as needed. However, elevated IOP can persist in some cases, suggesting either conversion or an underlying predisposition to develop POAG. Persistent glaucoma requires chronic medical management, and occasionally, laser treatment or standard filtration surgery.

BACKGROUND

The discovery of glucocorticoids was a major breakthrough in the treatment of inflammatory and autoimmune diseases, both systemic and ocular. However, their wide-

spread use has uncovered many serious side effects, including ocular hypertension and iatrogenic glaucoma. First reported by McLean, Stern, and Francois¹⁻³ in association with systemic administration of glucocorticoids, this secondary glaucoma is clinically similar to POAG and can cause similar irreversible visual field changes. Numerous reports, summarized in several detailed reviews,⁴⁻⁷ followed this initial discovery, documenting the development of steroid-induced ocular hypertension and secondary glaucoma with various glucocorticoids and routes of administration.

In the early 1960s, Armaly⁸ and Becker⁹ independently studied the effect of the potent glucocorticoids dexamethasone and betamethasone on IOP. Topical application of 0.1% formulations three to four times a day for 4 to 6 weeks produced three levels of response in the normal population: (1) 4 to 6% of individuals, termed "high responders," developed pressures above 31 mm Hg, or increases greater than 15 mm Hg above baseline; (2) one third of the population were "moderate responders," with pressures between 20 and 31 mm Hg, or pressure rises of 6 to 15 mm Hg; and (3) the remainder were "nonresponders," with IOPs less than 20 mm Hg and pressure increases less than 6 mm Hg.

When retested for steroid response, the nonresponder and moderate responder groups showed some variability in the magnitude of IOP elevation. However, greater than 98% of those individuals initially categorized as high responders remained either high or moderate responders.¹⁰ Although initial reports suggested that steroid responsiveness was inherited in a simple Mendelian manner,⁹ results of twin studies and the variable reproducibility of the steroid response have challenged this view.^{10,11} However, there still remains a strong link between steroid-induced ocular hypertension and POAG.^{6,7}

Administration of topical ocular glucocorticoids to patients with POAG produces a moderate to high response in nearly all subjects,^{12,13} and descendants of

POAG patients demonstrate a higher rate of steroid response than the general population.^{14,15} Finally, both prospective and retrospective clinical studies indicate that normal individuals classified as high steroid responders are more likely to develop POAG.^{16,17} These findings have led some to suggest that testing for steroid responsiveness may identify patients at risk for developing POAG. However, this has not become routine practice because of variability in the extent of the response¹⁰ and the perceived potential risk to normal individuals.

Among other groups of patients, both diabetics¹⁸ and high myopes¹⁹ also have higher rates of steroid responsiveness compared with the general adult population. Studies in children are conflicting. Whereas one study of Israeli children reported lower rates of steroid responsiveness,²⁰ rates in Japanese²¹ and Chinese²² children may be higher.

In addition to the responder status of the patient, the development of steroid-induced ocular hypertension also depends on the potency, duration, and dose of the steroid; its route of administration; and its ability to enter the eye.⁶ In general, those agents with the greatest anti-inflammatory efficacy and the highest affinity for the glucocorticoid receptor are most likely to induce ocular hypertension. Routes most apt to induce ocular hypertension are topical ocular administration as well as intraocular or periocular injections. The steroid response can also develop after receiving systemic glucocorticoids, or glucocorticoids applied to the skin, intranasally, or by inhalation.^{4,6}

PEARL... The development of steroid-induced ocular hypertension depends on family history and on the potency, duration, and dose of the steroid; its route of administration; and its ability to enter the eye.

Topical ocular steroids can also generate ocular hypertension in rabbits,^{23,24} cats,^{25,26} and monkeys.^{26,27} In monkeys, approximately 40% of otherwise normal animals develop increased IOP. This response is both reversible and reproducible.²⁸

PATHOPHYSIOLOGY

Steroids cause a number of cellular, biochemical, and molecular changes in the TM.⁷ One or more of these changes, many of which resemble those of POAG, could produce increased resistance to aqueous humor outflow, elevated IOP, and, eventually, glaucomatous optic nerve damage (Table 18-1).

Human eyes with steroid-induced glaucoma have increased deposition of extracellular material in the trabecular beams, as well as fingerprint-like deposits in the uveal meshwork and fibrillar deposits in the juxtanacanalicular tissue of the TM (Fig. 18-1A–D).^{29–31} Tissue culture experiments using isolated, human anterior segments in a perfusion chamber show that glucocorticoids can have

TABLE 18-1 EFFECTS OF GLUCOCORTICOIDS ON THE TRABECULAR MESHWORK

TM Cell Function	Inhibition of proliferation and migration ^{41,43} Inhibition of phagocytosis ^{43,44} IOP elevation and decreased hydraulic conductivity ^{*31,46}
TM cell morphology	"Activation" of TM cells (increased endoplasmic reticulum, Golgi complexes, and secretory vesicles) ^{*29,33} Increased TM cell size and nucleus size ³³ Increased capacity for biosynthesis ³³
TM extracellular matrix (ECM)	Increased deposition of ECM material in TM ^{*29–31} Increased expression of fibronectin, * laminin, collagen, and elastin ^{34–37} Decreased expression of t-PA and MMPs ^{7,39–40} Altered expression of glycosaminoglycans (decreased hyaluronic acid and increased chondroitin sulfate) ^{*7,38} Thickening of trabecular beams ^{*29–31}
TM cytoskeleton	Formation of cross-linked actin networks ^{*33,41} Increased expression of select actin-binding proteins Generation of microtubule tangles ³³ Increased resistance to cytoskeletal disruption
TM cell junctional complexes	Altered gap-junction morphology Altered expression of the tight junction protein ZO-1 ⁴⁶ Altered expression of select integrins ^{35–36}
TM cell gene expression	Increased expression of the glaucoma gene MYOC (<i>TIGR</i>) ^{*7,48,49,53} Increased expression of select ECM molecules ^{34–37} Decreased expression of MMPs ^{7,39–40}

* Indicates alterations observed in primary open-angle glaucoma. TM, trabecular meshwork; IOP, intraocular pressure; t-PA, tissue plasminogen activator; TIGR, trabecular meshwork induced glucocorticoid response; MMP, matrix metalloproteinase.

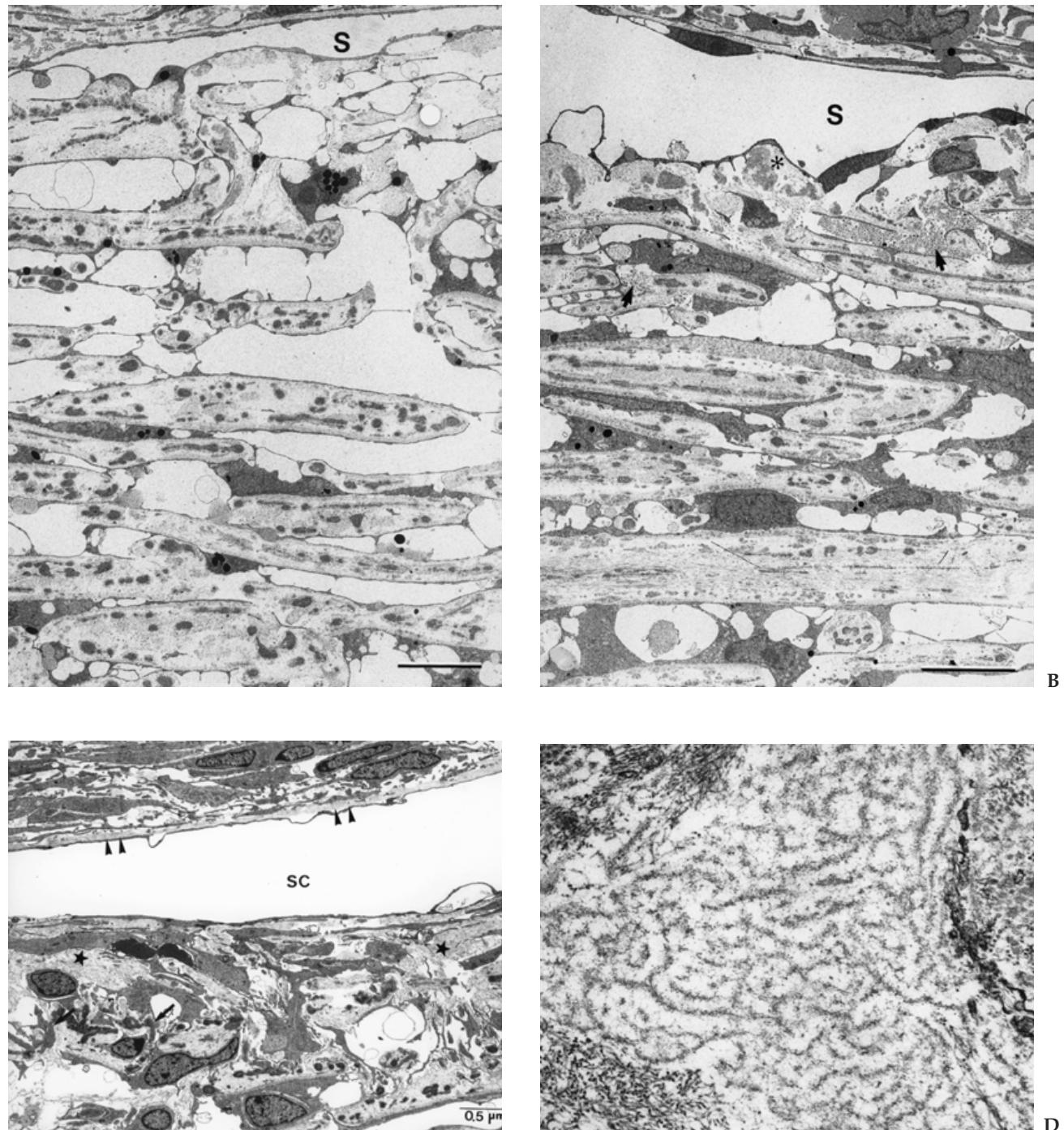


FIGURE 18-1 Morphological effects of glucocorticoids on trabecular meshwork tissue. (A) Transmission electron microscopy of the outflow pathway of a normal perfusion-cultured human eye. (B) The outflow pathway of a perfusion-cultured human eye with DEX-induced ocular hypertension, showing accumulation of fine fibrillar material (asterisk) and cellular debris (arrows). (C) The trabecular meshwork (juxtaganicular tissues and canal of Schlemm) of a 60-year-old patient with steroid-induced glaucoma from systemic prednisolone administration. Fine fibrillar extracellular material (star) appears within the juxtaganicular tissue and is increased adjacent to the outer wall endothelium (arrowheads). (D) Higher magnification of fingerprint-like extracellular material in the trabecular meshwork of a 13-year-old patient with glaucoma induced by topical ocular steroids. SC, Schlemm's canal. [(A) and (B) were reproduced with permission from Clark AF, Wilson K, deKater AW, Allingham RR, McCartney MD. Dexamethasone-induced ocular hypertension in perfusion cultured human eyes. *Invest Ophthalmol Vis Sci* 1995;36:478–489. (C) and (D) courtesy of Douglas Johnson, M.D., and reproduced with permission from Johnson D, Gottanka J, Flugel C, Hoffman F, Fluta T, Lutjen-Drecoll E. Ultrastructural changes in the trabecular meshwork of human eyes treated with glucocorticoids. *Arch Ophthalmol* 1997;115:373–383.]

direct effects on the TM.³¹ Thirty percent of such eyes develop ocular hypertension, similar to the steroid response rate in the normal human population. This elevated IOP is associated with increased deposition of extracellular matrix molecules, which has also been reported in the outflow pathway of patients with POAG.³²

SPECIAL CONSIDERATION

Corticosteroids produce several alterations in the TM that also occur in POAG. These include "activation" of TM cells, increased deposition of extracellular matrix material, alterations of the trabecular cell cytoskeleton, and increased expression of the glaucoma gene, myocilin.

Steroids can cause a number of cellular and biochemical changes in the TM, and the challenge is to determine which of these produce ocular hypertension and steroid-induced glaucoma. Steroids can directly affect the morphology of TM cells. This includes increasing nuclear and cell size and increasing the endoplasmic reticulum, Golgi complex, and secretory vesicles, all of which suggest activation of TM cells and an increase in their protein biosynthetic capacity.³³

Several biochemical studies in TM cells now support these morphologic findings, showing that steroid treatment increases the production of extracellular matrix (ECM) proteins,^{34–37} and alters expression of glycosaminoglycans.^{7,38} In addition, glucocorticoids may further encourage the deposition of ECM molecules in the meshwork by suppressing the expression of extracellular proteinases,^{7,39,40} which normally help turn over the ECM.

Steroids can produce a dramatic reorganization of the TM cell cytoskeleton.^{33,41} In glucocorticoid-treated TM cells, the actin microfilament network, normally organized into bundles of filaments, become rearranged into geodesic dome-like structures, known as cross-linked actin networks (CLANs) (Fig. 18–2A,B). The time-course for the formation and reversibility of CLANs closely correlates with that for the induction of glucocorticoid-mediated ocular hypertension.⁴¹ CLANs also appear to occur in TM cells isolated from donors with POAG.⁴²

Steroid-induced alterations in the TM cytoskeleton may lead to decreased proliferation,^{41,43} migration,⁴¹ and phagocytosis^{43,44} of TM cells. Reduced proliferation and migration likely produce the diminished cellularity seen in the TM of patients with steroid-induced glaucoma. Because these cells are normally highly phagocytic and provide a "self-cleaning filter" function to the TM, inhibition of phagocytosis may lead to progressive accumulation of extracellular debris, a "clogging" of the meshwork, and increased aqueous outflow resistance.⁴⁵

Steroids can also alter gap junctions (protein complexes that couple TM cells together) and mediate cell-to-cell com-

munication. In addition, steroids may tighten connections between cells and increase aqueous outflow resistance.⁴⁶ Glucocorticoids also can change the expression of several TM cell integrins,^{35,36} which are ECM receptors found in the cell membrane linked to the actin cytoskeleton, further affecting TM cell function and migration.

The recent discovery of the first glaucoma gene⁴⁷ presents another potential connection between POAG and steroid-induced glaucoma. This gene, variously named *GLC1A*,⁴⁷ *TIGR* (trabecular meshwork induced glucocorticoid response),^{48,49} and *MYOC* (the current, preferred name),⁵⁰ is a glucocorticoid-induced gene expressed in the TM. Initially discovered as the gene responsible for the autosomal dominantly inherited form of juvenile glaucoma, the myocilin gene is involved in a small, approximately 4%, subset of adult onset POAG.^{51,52} Specific mutations of this gene correlate with the development of a more severe, juvenile-onset type of glaucoma, whereas other mutations appear to cause milder, later-onset disease.⁵² Increased myocilin expression has also been reported in the TM of patients with several different types of glaucoma.⁵³

Myocilin (TIGR) initially was characterized as a protein induced by glucocorticoids in cultured TM cells (Fig. 18–3).⁴³ Although its function is currently unknown, myocilin appears in both intracellular and extracellular forms and is expressed in many ocular and nonocular tissues. Myocilin has also been found in cells of the optic nerve head,⁵⁴ where it may play a role in glaucomatous optic nerve damage.

Recent work has shown that glaucomatous mutations in *MYOC* prevent myocilin from being secreted from TM cells.^{53a} In addition, mice^{53b} and humans^{53c} lacking both copies of the *MYOC* gene do not appear to develop glaucoma. These data suggest that glaucomatous mutations in *MYOC* cause a gain of function phenotype, possibly due to an inadequate ability of the TM to handle misfolded mutant myocilin, leading to defective TM cell function.

Some investigators suggest that myocilin is responsible for glucocorticoid-induced ocular hypertension^{43,48,49} and speculate that excessive production of myocilin leads to increased aqueous outflow resistance. Although the time-course and dose-response characteristics of myocilin induction in cultured TM cells closely mimic the induction of glucocorticoid-induced ocular hypertension, it is not known if myocilin is responsible for, or merely associated with, the steroid response. Genetic studies have not revealed any mutations in the coding region of the myocilin gene to account for this response.^{28,55}

CONTROVERSY

There are no definitive data that differentiate whether myocilin is responsible for, or merely associated with, glucocorticoid-induced ocular hypertension.

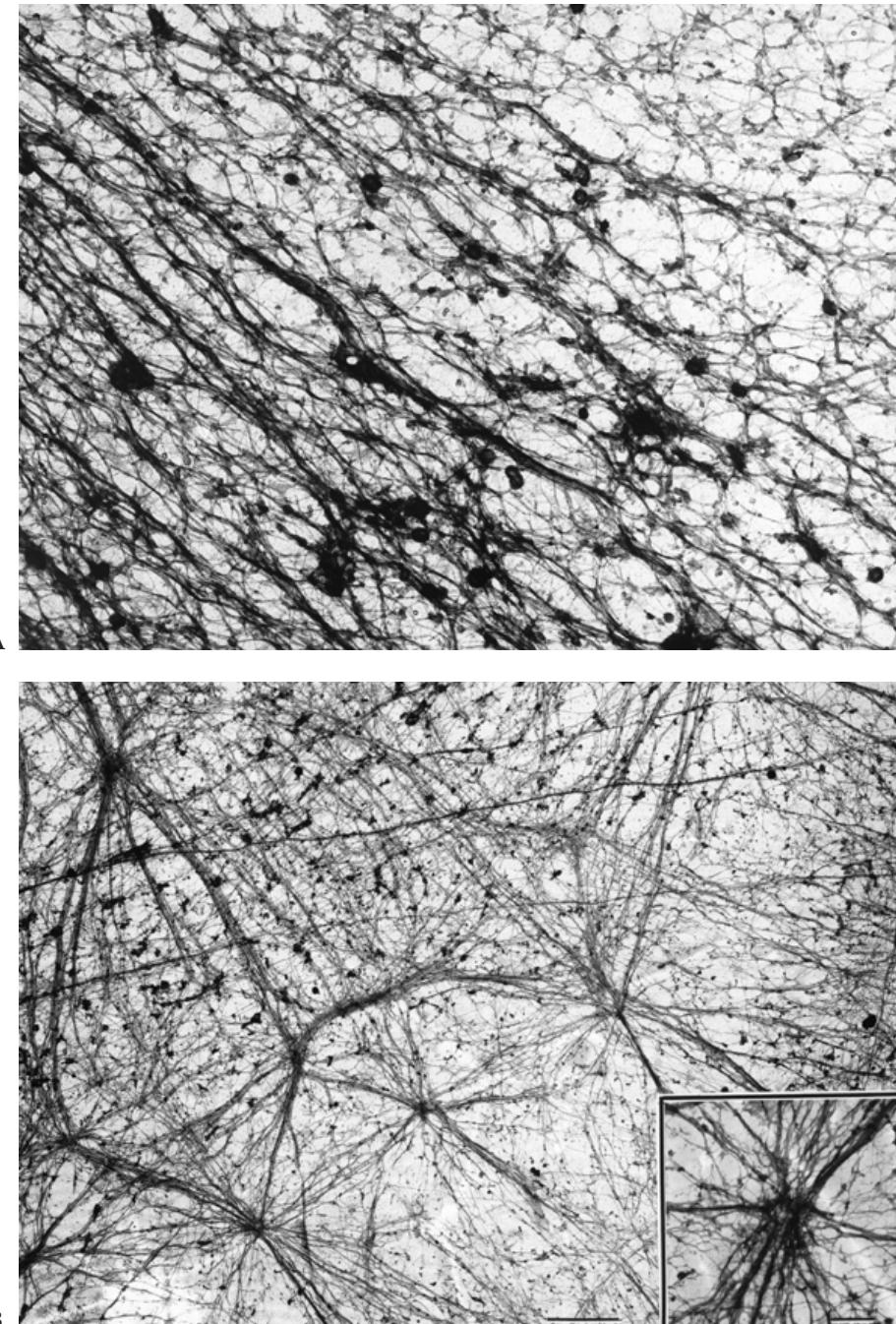


FIGURE 18-2 Effect of glucocorticoids on trabecular meshwork cell cytoskeleton. (A) Transmission electron microscopy (TEM) evaluation of normal TM cell showing actin microfilament bundles forming linear arrays of stress fibers. (B) TEM showing DEX-induced reorganization of microfilaments into geodesic dome-like structures called cross-linked actin networks (CLANS). [Reprinted with permission from Clark AF, Wilson K, McCartney MD, Miggans ST, Kunkle M, Howe W. Glucocorticoid-induced formation of cross-linked actin networks in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1994;35:281–294.]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Patients with steroid-induced glaucoma have relatively few symptoms (Table 18-2). The IOP rise is generally gradual and painless, although rare patients experience a typical brow ache. Decreased visual acuity usually results from associated subcapsular cataract, the underlying

condition that necessitated steroid treatment or, rarely, from end-stage optic nerve damage.

Eyes with steroid-induced glaucoma are quiet, with clear corneas (unless bedewed from elevated pressure) and open, normal-appearing anterior chamber angles. It normally takes at least several days, and usually weeks, to develop ocular hypertension from steroid treatment,

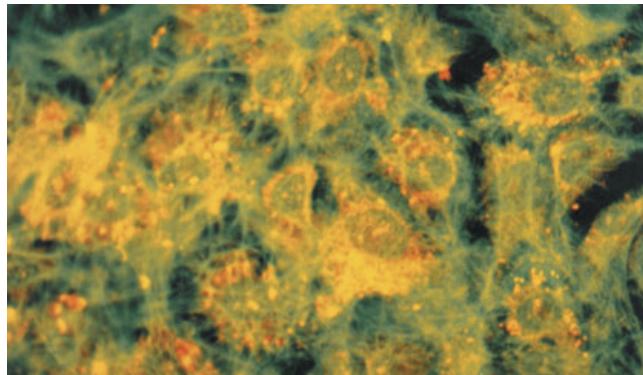


FIGURE 18-3 Expression of the glaucoma gene MYOC in cultured human trabecular meshwork (TM) cells treated with dexamethasone for 2 weeks. Myocilin is found intracellularly as discrete particles (stained red-yellow) surrounding the nucleus. Actin microfilaments are stained green. In many of the TM cells, myocilin is found inside “cages” of cross-linked actin networks (CLANs).

and the IOP usually remains elevated, often in the 30 to 60 mm Hg range, for as long as the patient receives the agent. Although steroid-induced ocular hypertension is generally reversible, several reports document continued IOP elevation, even long after withdrawal of the steroid.^{56–58} This may depend in part on the dosage and duration of treatment because eyes with longer treatment are more likely to demonstrate a sustained pressure rise.

The optic nerve damage from steroid-induced glaucoma appears typical for all glaucomas, ranging from generalized cupping to vertical elongation of the optic cup and focal notching, erosion, and undermining of the disc margin (Fig. 18-4A–C). Visual field loss appears similarly characteristic. Although the steroid-induced IOP elevation is reversible in most cases, damage to the optic nerve and visual field is not.

The major differential diagnosis of steroid-induced glaucoma is POAG (Table 18-3). The history of steroid use can be key to making this differentiation. Because many people do not include topical skin preparations when responding to the general query regarding what medicines they take, they must be specifically questioned about topical as well as ocular and systemic medications. If the patient does use topical corticosteroids, determining the strength of preparation, the site of application, and the frequency is important because the extent of pressure rise can be proportional to the dose received by the eye. As stated earlier, patients with a family history of glaucoma are more likely to develop a steroid response, as well as POAG.

The clinical course may also help make the diagnosis, which may only be evident after the suspected offending agents are discontinued. Onset of IOP elevation generally occurs after days to weeks of administration, although acute increases (within hours) have been reported in POAG patients.⁵⁹ In general, IOP returns to normal following discontinuation of glucocorticoids.

TABLE 18-2 DIAGNOSIS OF GLUCOCORTICOID-INDUCED GLAUCOMA

History	History of steroid use (any route) Family history of glaucoma or steroid-induced glaucoma
Symptoms	Generally few Decreased vision secondary to corneal edema, end-stage visual field loss, steroid-induced cataract or the underlying condition
Signs	Occasional epithelial edema from IOP Open angle, normal appearance Elevated IOP, may be marked IOP elevation generally resolves following discontinuation of corticosteroids Typical glaucomatous optic nerve damage and visual field loss

IOP, intraocular pressure.

Because IOP may not revert to normal, it may not be possible to determine if these patients represent true, irreversible steroid-induced glaucoma or latent cases of POAG that either developed coincidentally with the steroid use, or were unmasked by these drugs. Because IOP elevation is often variable, a rechallenge with the offending agent may be the only way to confirm the diagnosis.

In general, ciliary flush, cells, and flare in the anterior chamber and, in advanced cases, anterior and posterior synechiae, will distinguish uveitic glaucoma from steroid-induced glaucoma.

However, confusion may arise when treating active uveitis with intense topical corticosteroids. In this situation, IOP may initially be low from the inflammation itself, but will then increase due to suppression of the inflammation and recovery of aqueous humor production. This can result in a significant pressure rise, which may be interpreted as a steroid response. However, the relative rarity of steroid-induced glaucoma, coupled with the need for aggressive management of ocular inflammation, argues in favor of treating the uveitis until it is substantially resolved. The steroid dosage can then be reduced, changed to a less potent corticosteroid, or discontinued in favor of a “steroid-sparing” agent. Some cases require standard glaucoma therapy to allow time to treat the inflammation properly and wean the patient off the corticosteroids.

PITFALL... Steroid treatment of acute uveitis can suppress inflammation and allow the recovery of aqueous humor production. The resulting increase in IOP may be mistaken for steroid-induced glaucoma.

Other, less common, forms of uveitis may also present diagnostic confusion, such as glaucomatocyclitic crisis, or Posner-Schlossman syndrome. This condition, dis-

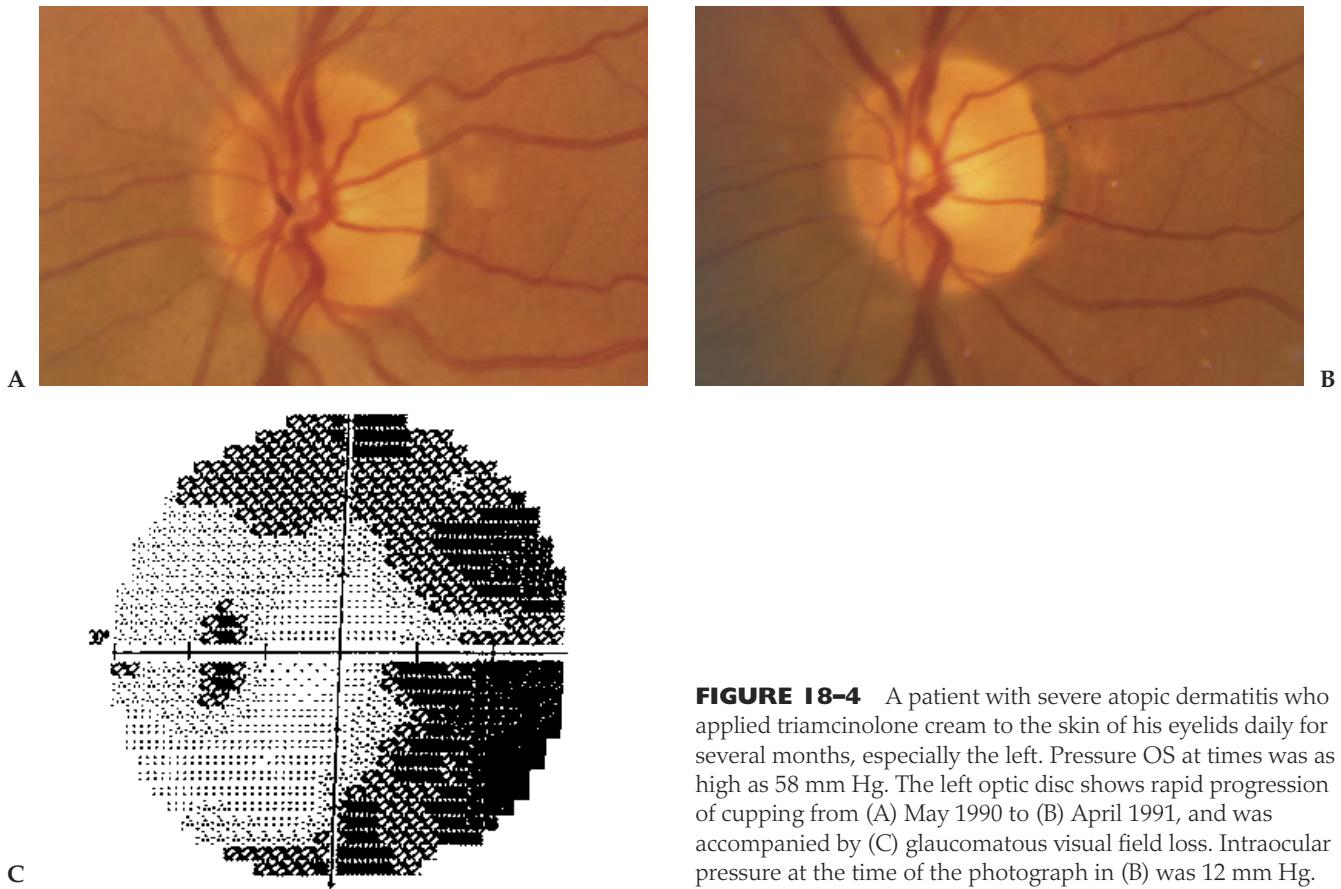


FIGURE 18-4 A patient with severe atopic dermatitis who applied triamcinolone cream to the skin of his eyelids daily for several months, especially the left. Pressure OS at times was as high as 58 mm Hg. The left optic disc shows rapid progression of cupping from (A) May 1990 to (B) April 1991, and was accompanied by (C) glaucomatous visual field loss. Intraocular pressure at the time of the photograph in (B) was 12 mm Hg.

cussed more fully in Chapter 26, often lacks the traditional signs of uveitis, with the exception of mild anterior chamber reaction, discrete keratic precipitates, and the remarkable elevation in IOP. Treatment with corticosteroids typically helps control the inflammation and, secondarily, the glaucoma.

Steroid-induced glaucoma may paradoxically resemble low-tension glaucoma if it produces optic nerve damage, which is then detected after the patient has discontinued the corticosteroids and the pressure has returned to normal (Fig. 18-4A–C). Again, the history of steroid use is crucial to making the correct diagnosis.

TABLE 18-3 DIFFERENTIAL DIAGNOSIS OF STEROID-INDUCED GLAUCOMA

Condition	Differentiating Features
Primary open-angle glaucoma	No steroid use May be difficult to differentiate in cases that do not resolve after discontinuing corticosteroids
Uveitic glaucoma	Anterior chamber cells, flare Keratic precipitates, synechiae Treatment of uveitis with corticosteroids may produce elevated IOP due to recovery of ciliary body function, and may be mistaken for a steroid response Therapeutic dilemma arises from need to treat ocular inflammation with corticosteroids, both of which may elevate IOP
Glaucomatocyclitic crisis	Subtle anterior chamber reaction IOP elevation episodes independent of steroid use
Normal-tension glaucoma	Glaucomatous optic nerve damage with normal IOP may resemble steroid-induced glaucoma following discontinuation of steroids and normalization of IOP Lack of history of corticosteroid use
Juvenile glaucoma	Anterior iris insertion with flat contour Patient age

IOP, intraocular pressure.

Juvenile glaucoma may occasionally also be confused with steroid-induced glaucoma. The IOP rise may be marked, with an open angle and quiet anterior chamber. Subtle signs, such as anterior insertion of the iris and a flat iris plane, generally help with this differentiation (see Chapter 17).

MANAGEMENT

Prevention remains the most effective treatment for steroid-induced glaucoma (Table 18-4). This involves using these potent medications only when indicated and limiting dosages to those necessary to achieve the desired effect. However, necessary corticosteroids should never be withheld out of concern for creating steroid-induced glaucoma.

When corticosteroid treatment is necessary, particularly with potent topical ocular agents and periocular injections, the physician should always monitor the patient for steroid-induced glaucoma. This includes obtaining baseline IOP measurements, mostly to rule out pre-existing glaucoma. Pressure monitoring should initially occur every 4 to 6 weeks, decreasing to once every several months after an initial response has been ruled out. Typically, if steroids are prescribed for an ocular problem, the examinations necessary to monitor the ocular condition, with IOP measurements incorporated at every opportunity, are sufficient to monitor the patient for steroid-induced glaucoma.

SPECIAL CONSIDERATION

Discontinuing corticosteroids can be complicated by the need to treat the underlying condition, the unpredictable rate at which the glaucoma resolves, and the fact that the glaucoma can persist long after the steroids are stopped.

TABLE 18-4 MANAGEMENT OF STEROID-INDUCED GLAUCOMA

Prevention	Avoid unnecessary or prolonged use of corticosteroids, particularly in patients with a family history of glaucoma Recognize the use of steroids by any route Recognize the relative tendency of different steroid preparations to cause glaucoma
Treatment	Carefully monitor patients on corticosteroids, especially those with a family history of glaucoma Discontinue steroids (if possible) Use alternative, "steroid-sparing" medications Suspect POAG if IOP remains elevated after discontinuing corticosteroids Standard medical, laser, and surgical management to prevent glaucomatous optic nerve damage

IOP, intraocular pressure; POAG, primary open-angle glaucoma.

Although discontinuing steroid treatment may offer the most logical management for steroid-induced glaucoma, this is often not possible. Under these circumstances, the steroids must simply be continued, often at an aggressive pace (such as with uveitis), to get the inflammation under control as rapidly as possible. Consultation with physicians responsible for any systemic steroid administration is also necessary, at least to alert them to the problem and request that they taper and discontinue steroids as rapidly as possible. In the meantime, the glaucoma itself must be treated medically, at least temporarily, to protect the optic nerve.

Discontinuing steroids can also present other problems. Although stopping topical medications is relatively simple, the rate at which the glaucoma resolves is unpredictable, and there is no consensus as to how long to wait before deciding that removing steroids has resolved the situation. If the glaucoma results from a periocular corticosteroid injection, surgical excision of the steroid can be done, but usually involves removing associated scar tissue, Tenon's capsule, and fat.

Unfortunately, stopping corticosteroids does not always resolve the glaucoma. This circumstance may arise simply because the glaucoma has resulted as a complication of the underlying condition, such as uveitis, leaving permanent functional trabecular damage. Alternatively, the steroid may "unmask" a patient's latent POAG that then simply persists.

Medical management of steroid-induced glaucoma is usually undertaken to protect the optic nerve, particularly if it is already severely damaged. The extremely high elevation of IOP seen in many of these cases may also necessitate treatment even if the optic nerve appears healthy.

Medical treatment is usually a temporizing measure until steroids can be safely discontinued. This includes the entire array of available topical antiglaucoma medications, beginning with aqueous humor suppressants. These include adrenergic antagonists, followed by either alpha agonists or topical carbonic anhydrase inhibitors.

Latanoprost in this condition specifically has not been thoroughly evaluated. However, this, as well as miotics, may be effective, particularly as additive agents. Although long-term complications with either of these agents are generally not a concern in this self-limited condition, both may be contraindicated in patients with uveitis or trauma.

The efficacy of argon laser trabeculoplasty (ALT) in this condition may be slightly less than in other forms of open-angle glaucoma. However, it is particularly attractive when considered as a means of avoiding filtration surgery, particularly if corticosteroids can be discontinued and the need for chronic treatment is limited.

Surgical management consists primarily of filtration surgery, and its success is essentially the same as for other open-angle glaucomas. This option should be reserved for those cases in which medications and laser have failed to control the pressure, and in which resolution through discontinuation of the corticosteroids is not anticipated to occur soon enough to protect the optic nerve.

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PIGMENT DISPERSION SYNDROME AND PIGMENTARY GLAUCOMA

Donald A. Abrams, M.D.

Pigment dispersion syndrome (PDS) probably results from chronic rubbing of the iris pigment epithelium on the lens zonules. This produces radial iris transillumination defects, and pigment release and deposition on the cornea, iris, and lens, and in the trabecular meshwork. Usually diagnosed in the third or fourth decade of life, active pigment dispersion generally increases over the next two decades and may diminish after that, presumably due to enlargement of the lens, relative pupillary block, and gradual "lifting" of the peripheral iris away from the zonules.

Twenty-five to 50% of patients with PDS can develop pigmentary glaucoma. Although anecdotal reports suggest that prophylactic miotic therapy and peripheral iridotomy can decrease or stop further pigment dispersion, no studies have yet shown that these interventions reliably prevent the development of glaucoma.

Pigmentary glaucoma is generally more resistant to medical therapy and requires earlier surgery than primary open-angle glaucoma. However, the prognosis is generally good. Early diagnosis, appropriate follow-up, and treatment of this glaucoma depend on the recognition of the often subtle, anterior segment changes of pigment dispersion syndrome.

BACKGROUND

Krukenberg first noted pigment dispersion in the anterior segment of the eye in 1899 and described the vertical pigment deposit on the corneal endothelium that now bears his name. In the 1940s, Sugar described cases of glaucoma caused by heavy pigmentation of the trabecular meshwork and coined the term *pigmentary glaucoma*.^{1,2} He later reviewed 147 cases of pigmentary glaucoma and noted additional associations with myopia, a greater prevalence in males, and onset in younger individuals.³

In 1981, Scheie and Cameron studied 407 patients with pigment dispersion syndrome.⁴ They found a 65% prevalence of myopia, an equal sex distribution, a higher incidence of associated glaucoma in the male patients, and a significantly decreased age of onset of glaucoma compared with chronic open-angle glaucoma. They also noted that the glaucoma was worse in the more heavily pigmented eye in patients with bilateral disease.

In a population undergoing glaucoma screening, Ritch et al found a prevalence of 2.45% of pigment dispersion syndrome in whites.⁵ It has been estimated that 0.9 to 2.5% of glaucoma patients in the United States have pigmentary glaucoma. Although thought to be almost nonexistent in blacks, Semple and Ball found 20 patients with pigment dispersion syndrome out of 1217 black patients examined.⁶ From this group, they observed a preponderance of older age, hyperopia, and male gender, but no iris transillumination defects.

Although the age of onset is unknown, pigment dispersion syndrome is most frequently diagnosed in the third and fourth decades.⁷ In unpublished data, Ritch found no cases on slit-lamp screening of 311 New York City high school juniors, suggesting that detectable pigment dispersion is uncommon before age 20.⁵

Glaucoma may develop in 25 to 50% of patients with pigment dispersion syndrome,^{8,9} and young age, male gender, myopia, and white race appeared to be the most significant risk factors. This disease comprises about 1.5% of glaucomas in the West, usually affecting young adults 20 to 45 years of age. One study found that the diagnosis of pigmentary glaucoma was made earlier in men and that men required more aggressive medical and surgical therapy.¹⁰ Another noted that, among pigmentary glaucoma suspects, the incidence of progression to pigmentary glaucoma was the same for men and women.⁸

PEARL... Young male myopes are the most common group to develop pigment dispersion syndrome and its associated glaucomatous optic neuropathy.

In one study, with a follow-up of 17 years, about 35% of patients with pigment dispersion syndrome and ocular hypertension developed glaucomatous cupping and visual field loss.⁸ However, progression with age is not always inexorable, as many eyes demonstrate a reduction in pigment release over time.⁸

HEREDITY

Although the majority of pigment dispersion syndrome cases with glaucoma are sporadic, families with more than one member having pigment dispersion syndrome have been reported, including both autosomal recessive¹¹ and autosomal dominant¹² inheritance. One report has mapped a gene responsible for an autosomal dominant pigment dispersion syndrome to chromosome 7q35-q36.¹³

PATHOGENESIS

PATHOLOGY

In 1979, Campbell observed that pigment dispersion occurred in eyes that are larger than normal and tend to be myopic.¹⁴ Many of these eyes have a slightly concave peripheral iris that may rest on the zonules, allowing mechanical rubbing between the anterior packets of zonules and the peripheral iris during normal pupillary movement. Histologically, Campbell showed a groove in the stroma of the iris, as well as the loss of the pigmented neuroepithelium that was compatible with mechanical

damage, strongly supporting this as the cause of the loss of iris pigment and its release into the anterior and posterior chambers. Potash confirmed these findings with the ultrasound biomicroscope in 16 eyes with untreated pigment dispersion.¹⁵ He found midperipheral iris concavity in 56% of eyes, iridozonular contact in 25%, and iridociliary process contact in 75%.

The formation of iris concavity may not be a simple, passive result of anterior segment anatomy. Karickhoff¹⁶ and Campbell¹⁷ postulated a mechanism of "reverse pupillary block," where aqueous humor pressure in the anterior chamber exceeds that of the posterior chamber, possibly secondary to anterior movement of aqueous encouraged by blinking and aided by obstruction to aqueous humor outflow through the trabecular meshwork. This forces the iris posteriorly over the lens, where it acts as a "flap valve," preventing the return of aqueous to the posterior chamber. This would accentuate the concave iris configuration and iris-zonule contact.

Once the pigment is released from the iris pigment epithelium, it distributes throughout the anterior segment and onto the cornea, iris, lens, zonules, ciliary body, and trabecular meshwork. A fundamental question in this disease is whether the pigment loss from the posterior iris results simply from mechanical rubbing of the iris on the zonules,¹⁴ or if a primary iris pigment epithelial degeneration, or "abiotrophy," must also be present to allow the pigment release.^{18,19}

MECHANISM OF GLAUCOMA

Pigment deposition in the trabecular meshwork (Fig. 19-1A,B) causes elevated IOP and subsequent glaucomatous optic neuropathy. Alvarado and Murphy proposed a sequence of events leading to the development of glaucoma in pigment dispersion syndrome.²⁰ Phagocytosis

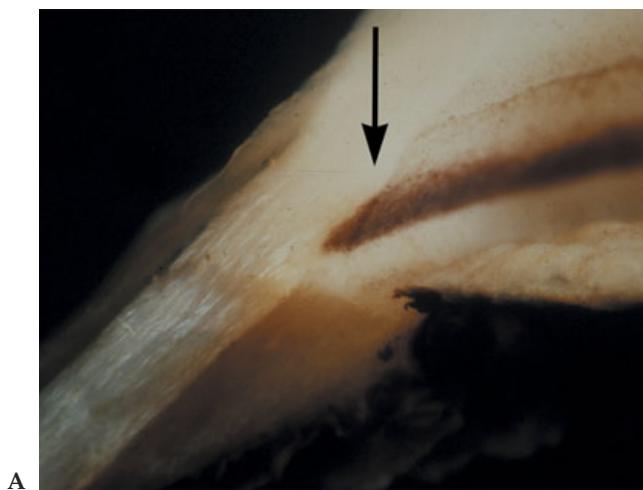
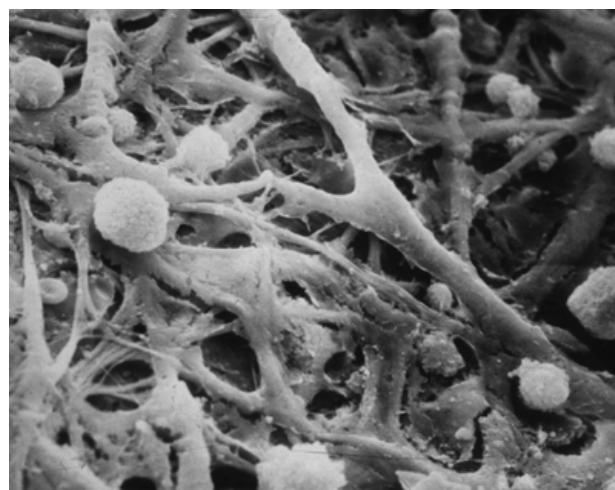


FIGURE 19-1 Pathological specimen of an eye with pigment dispersion syndrome. (A) Cross section through the angle (arrow) shows dense deposit of pigment throughout the thickness of the trabecular meshwork. (B) Scanning electron micrograph demonstrates pigment-laden macrophages within the inner trabecular beams. [(A) and (B) courtesy of W. Richard Green, M.D. (B) reprinted with permission, *A J Ophthalmol* 91:573–587.]



B

of pigment by trabecular endothelial cells leads to overload of these cells, producing cell injury and death, possibly via a free radical mechanism. Glaucoma follows due to dysfunction of the trabecular endothelium, secondary sclerosis of the trabecular meshwork, and loss of porosity of the uveoscleral and corneoscleral meshworks.

Epstein et al infused pigment particles isolated from the iris and ciliary body of enucleated cynomolgus monkey eyes into the anterior chamber of living cynomolgus monkeys and determined outflow facility both acutely and 1 week later.²¹ Outflow facility decreased 64% acutely in the pigment-perfused eyes compared with a 76% increase in the sham-manipulated fellow eyes. However, when outflow facility was measured 1 week later, it returned to baseline levels. Repetitive pigment perfusions similarly failed to produce any long-term abnormality in outflow facility. Their results suggest that other factors, in addition to pigment particle accumulation in the trabecular meshwork, may be involved in the mechanism of human pigmentary glaucoma.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although most patients with pigmentary glaucoma are asymptomatic, some report blurred vision and colored halos around lights after vigorous exercise.²² These symptoms are correlated with elevated IOP,²³ suggesting corneal epithelial edema as well as blurring from pigment dispersion within the anterior chamber, which is more likely after exercise in patients with pigment dispersion than control subjects.

Classic signs of pigment dispersion syndrome include bilateral, but often asymmetric, loss of pigment from the iris pigment epithelium. This typically appears on retroillumination as radial slitlike defects in the midperipheral region of the iris (Fig. 19–2A,B). This may be difficult to detect in brown irides, generally necessitating a strong, cen-

trally placed slit beam shorter than the pupil and dimming or eliminating ambient room light to aid contrast. Fine corneal endothelial pigment deposits appear as a vertical band 1 to 2 mm in width and 3 to 6 mm in height. The distinctive shape of these Krukenberg spindles (Fig. 19–3A–C) probably results from aqueous convection currents within the anterior chamber. This spindle may be seen by either direct or indirect illumination, sometimes aided by using the diffuse beam of the slit-lamp. Occasionally, a dilated pupil provides a uniform background against which the spindle is more easily seen by either method. Pigment “dusting” of the anterior surface of the iris is common and may occasionally appear as concentric rings of fine pigment that are densest in the peripheral furrows (Fig. 19–4).

SPECIAL CONSIDERATION

African Americans with pigmentary glaucoma often lack transillumination defects, due to thicker irides and more deeply pigmented iris stroma.

By gonioscopy, the trabecular meshwork contains a homogeneous, dense band of pigment (Fig. 19–5). This increased pigmentation may extend onto the anterior, nonpigmented meshwork in severely affected individuals as well as anterior to Schwalbe’s line, in a thin band called Sampaolesi’s line. Gonioscopy also reveals the posterior, concave iris contour, an effect that may also be appreciated with direct, slit beam examination (Fig. 19–6A,B). Pupillary dilation can release a “shower” of pigment into the anterior chamber, visible within the slit beam, and can allow the examiner to observe deposits of pigment on the lens zonules (Fig. 19–7), the peripheral lens capsule, and the anterior vitreous face.

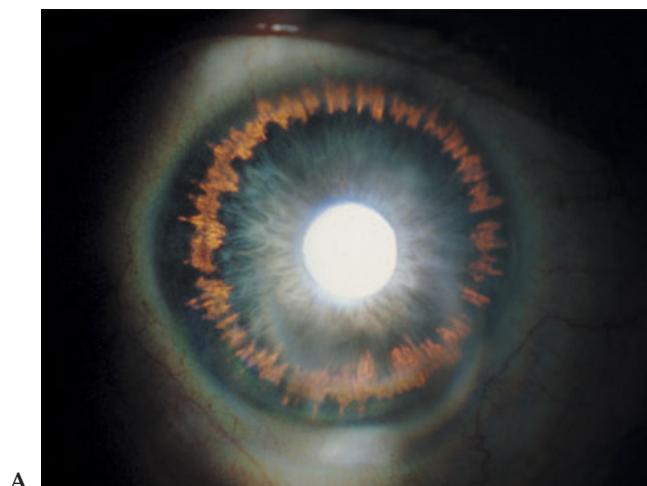
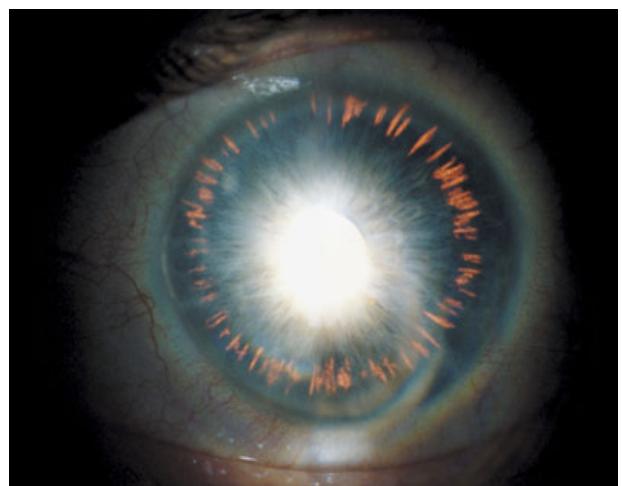
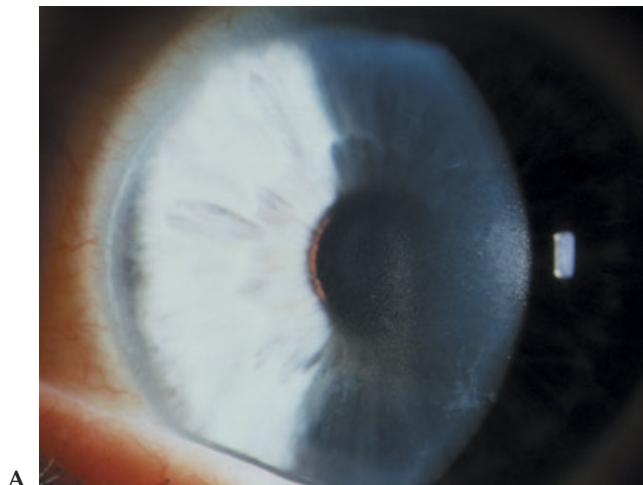
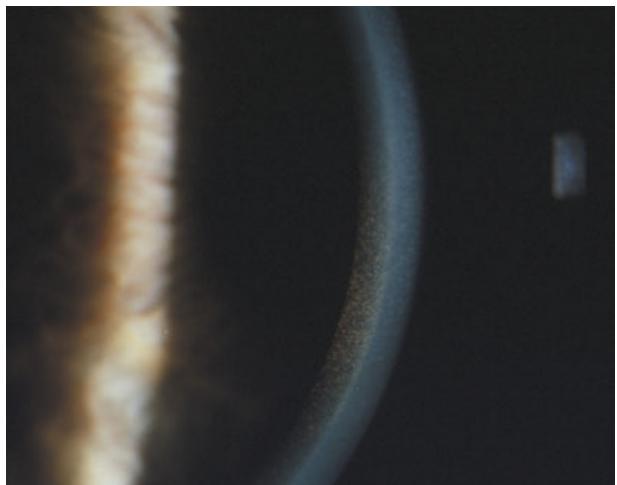


FIGURE 19-2 Typical radial, slitlike iris transillumination defects in a patient with pigmentary glaucoma demonstrates marked asymmetry between the (A) right and (B) left eyes.

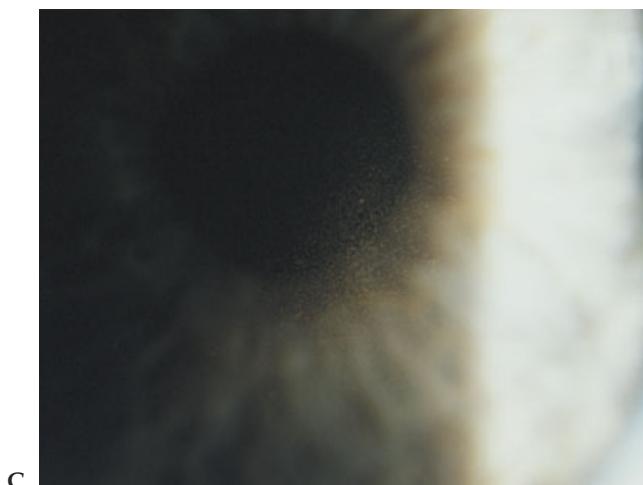




A



B



C

FIGURE 19-3 (A,B) Fine corneal pigment deposits seen on direct illumination demonstrates the vertical Krukenberg spindle configuration and position of the pigment on the corneal endothelium. (C) Fine pigment deposits are occasionally better seen with retroillumination.

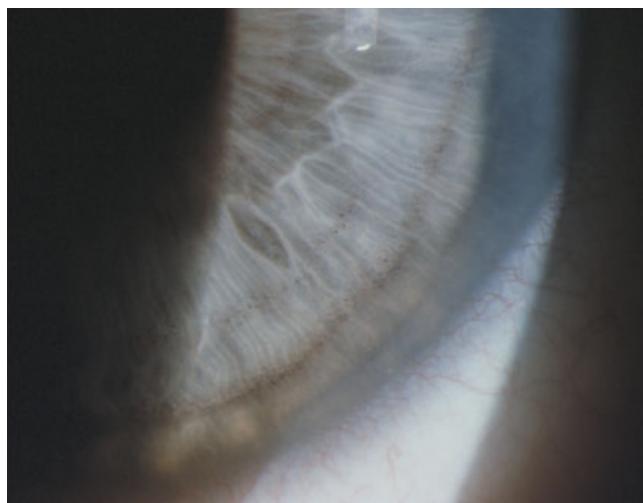


FIGURE 19-4 Pigment dusting on the anterior corneal stroma may deposit in concentric rings within the peripheral iris furrows.

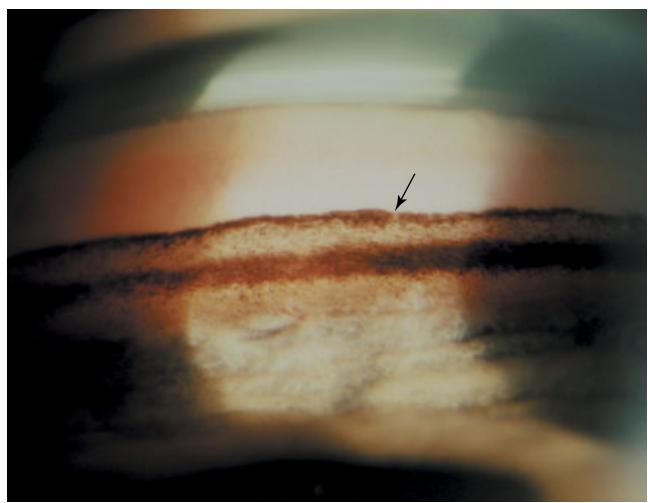


FIGURE 19-5 Gonioscopy typically reveals dense, uniform pigmentation of the trabecular meshwork. This may extend anteriorly onto Schwalbe's line, producing a second, thinner line of pigment, known as Sampaolesi's line (arrow).

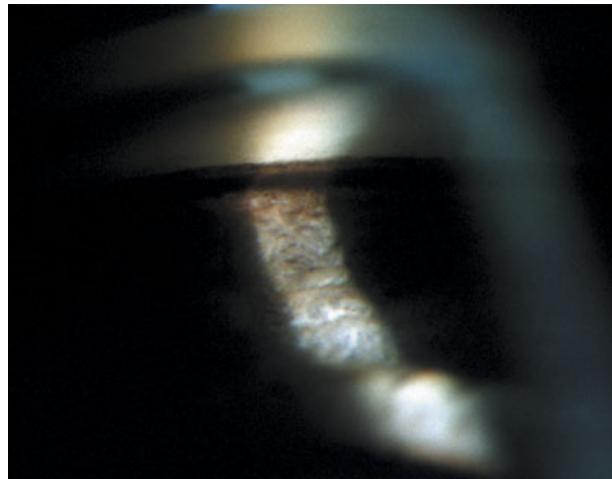
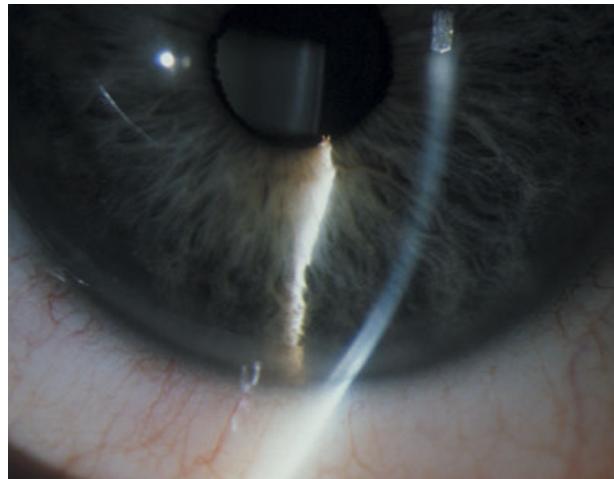
**A****B**

FIGURE 19-6 (A) Viewing the angle by gonioscopy with a slit beam reveals the extent of iris concavity, which can also be detected by (B) direct slit beam examination.

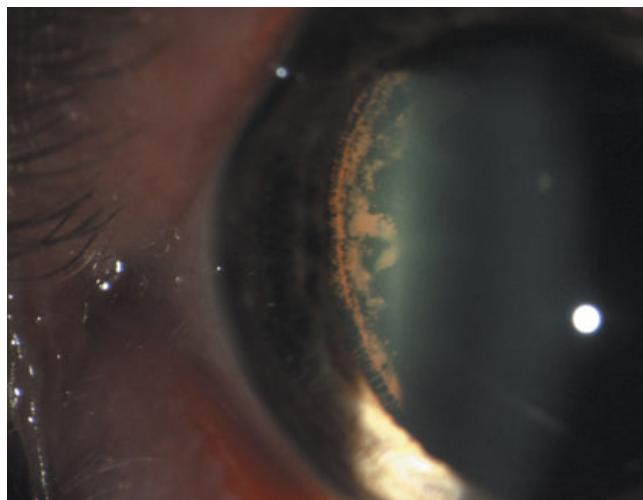


FIGURE 19-7 Pigment deposits on the posterior zonules and peripheral lens capsule.

High-resolution ultrasound biomicroscopy is a relatively new diagnostic device used for imaging the anterior segment of the eye²⁴ and allows *in vivo* visualization of posterior chamber structures. Potash et al have shown midperipheral iris concavity, iridozonular contact, and iridociliary contact in untreated eyes with pigment dispersion syndrome using this technique.

In eyes with pigment dispersion syndrome, the IOP remains normal. However, IOP may be significantly elevated by exercise, particularly in patients who report blurred vision following vigorous activity, and by cycloplegia, which releases ciliary muscle tone on the trabecular meshwork. Optic nerve damage varies with the extent of IOP elevation and its duration, and displays the typical features of glaucomatous optic neuropathy. IOP elevation is often more pronounced in the eye with more iris transillumination defects and greater trabecular meshwork pigmentation.

DIFFERENTIAL DIAGNOSIS

Several ocular conditions that may also be associated with glaucoma can resemble pigment dispersion syndrome and pigmentary glaucoma, either on the basis of iris transillumination defects or on increased pigmentation of the trabecular meshwork. However, each of these conditions possesses distinct and differentiating features.

Although patients with pseudoexfoliation syndrome have increased pigment deposition in the anterior segment, pigmentation in the angle tends to be less intense and more unevenly distributed than in pigmentary dispersion (Chapter 20). Pigment on the corneal endothelial surface is more evenly distributed than the vertically aligned Krukenberg spindle of pigment dispersion syndrome. Additionally, the iris transillumination defects, which are not slitlike, usually appear at the pupillary margin and do not extend to the iris midperiphery. Finally, pseudoexfoliation syndrome has the deposition of white

PITFALL... The deposition of pigment on the endothelial surface of the cornea (Krukenberg spindle) can be very subtle, and the diagnosis of pigment dispersion syndrome can be overlooked. The first signs in some of these patients may be iris transillumination defects and/or significant pigment deposition in the trabecular meshwork.

With advancing age, pigment dispersion syndrome and pigmentary glaucoma can regress slowly as the amount of pigment released from the iris decreases and the deposited pigment disappears, due to the eye's natural phagocytic mechanisms. It has been postulated that this reversion occurs in later years when there is gradual lens enlargement and pupillary miosis leading to increased pupillary block. Then the peripheral iris lifts off the zonules, making pigment dispersion less likely.¹⁴

flaky exfoliation material distributed in a characteristic fashion on the pupillary border and anterior lens surface. Pseudoexfoliation glaucoma usually does not present until after age 60 and is rare under age 40. Because pseudoexfoliation is often asymmetric, it can appear nearly unilateral in approximately half of patients.

In uveitic glaucoma, white cells floating in the anterior chamber can be mistaken for pigmented cells (see Chapter 26). Although uveitis can increase trabecular pigmentation, the pigment appears uneven and splotchy, unlike pigment dispersion, and may accompany keratic precipitates and anterior and posterior synechiae. Iris transillumination defects may also help differentiate uveitis from pigment dispersion. Herpes zoster keratouveitis may cause sectoral iris atrophy, and iris atrophy from herpes simplex keratouveitis is generally more diffuse. Both patterns are distinct from those of pigment dispersion syndrome and pigmentary glaucoma.

Peripheral iris and ciliary body cysts can also be associated with moderate amounts of pigment deposition in the anterior segment. However, although these eyes generally lack a Krukenberg spindle, they can have increased deposition of pigment in the angle. Identifying the cysts under the iris by gonioscopy and ultrasound biomicroscopy generally helps make this diagnosis.

Cataract extraction and posterior chamber lens implantation can also produce a form of pigmentary glaucoma.²⁵ In this situation, iris transillumination defects are limited to areas of surgical trauma and chronic rubbing of the lens on the iris pigment epithelium. They often correspond to the position of the haptics or optic edge, a pattern much different from that of pigment dispersion. Angle pigment tends to be more unevenly distributed than with pigment dispersion syndrome. All of these changes are more commonly noted in the operative eye, and usually with sulcus-fixated lenses.

Ocular melanomas of the iris and ciliary body can also present with pigment dispersion.²⁶ Here, pigmented tumor cells or pigment-laden macrophages appear in the anterior segment, causing a darkened trabecular meshwork, and melanomalytic glaucoma. These eyes lack Krukenberg spindles and transillumination defects, and careful fundus or ultrasound evaluation will generally reveal the intraocular tumor.

MANAGEMENT

The management of patients with pigment dispersion syndrome and pigmentary glaucoma includes careful monitoring and prophylaxis to limit the progression of the pigment dispersion itself, and treatment of elevated IOP to prevent optic nerve damage.

PROPHYLAXIS

Pigment dispersion syndrome patients present with normal IOPs without evidence of glaucomatous visual field

or optic nerve changes. The patients at greatest risk for glaucoma are young, male, and myopic, but all should be counseled with regard to the likelihood of developing glaucoma. Because up to 50% of pigment dispersion syndrome patients do eventually develop glaucoma,^{8,9} many may elect either medical or laser prophylaxis.

Miotics, which contract the pupillary sphincter, are thought to stretch the iris, lift it off of the zonular packets, and diminish loss of pigment from the posterior surface of the concave iris.¹⁵ In fact, eyes treated with pilocarpine are significantly less likely to develop exercise-induced pigment dispersion than eyes not treated with pilocarpine.

However, side effects may limit the use of miotics in this relatively young, myopic population. These include unacceptable blurred vision from induced myopia. Retinal detachment is another potential complication of miotic therapy, particularly given that myopes already have an increased tendency for retinal tears and detachments. Retinal detachment rates in pigment dispersion syndrome and pigmentary glaucoma are 6.6 and 7.6%, respectively.⁴ Careful retinal examination and prophylactic treatment of any peripheral retinal breaks should always precede the initiation of miotic therapy.

SPECIAL CONSIDERATION

Although miotic therapy may tighten the iris and prevent subsequent release of pigment from the posterior iris, it can produce severe visual blurring from induced myopia and has the potential to cause retinal detachment in these young, myopic patients.

The efficacy of miotics in preventing the development of pigmentary glaucoma has been difficult to document. One retrospective study noted that 74% of the patients with pigment dispersion syndrome who eventually developed pigmentary glaucoma were initially treated with miotics before they developed glaucomatous changes in the optic nerve and visual field.⁸ Although this may indicate that the assumed mechanism of pigment dispersion is incorrect, it is also possible that these patients were not started on miotic agents early enough in the course of the disease.

Laser iridotomy, which should circumvent the reverse pupillary block mechanism already noted, can also flatten the iris contour.²⁷ This prevents the formation of a concave iris and its rubbing on the zonular packets (Fig. 19-8A,B). This effect is generally more predictable in the eyes with deeper, more concave irides. Although many anecdotal cases indicate that iridotomy can decrease or stop further dispersion of pigment in these patients, prospective studies are currently lacking. Because successful flattening of the iris will not immediately lower chronically elevated IOP,

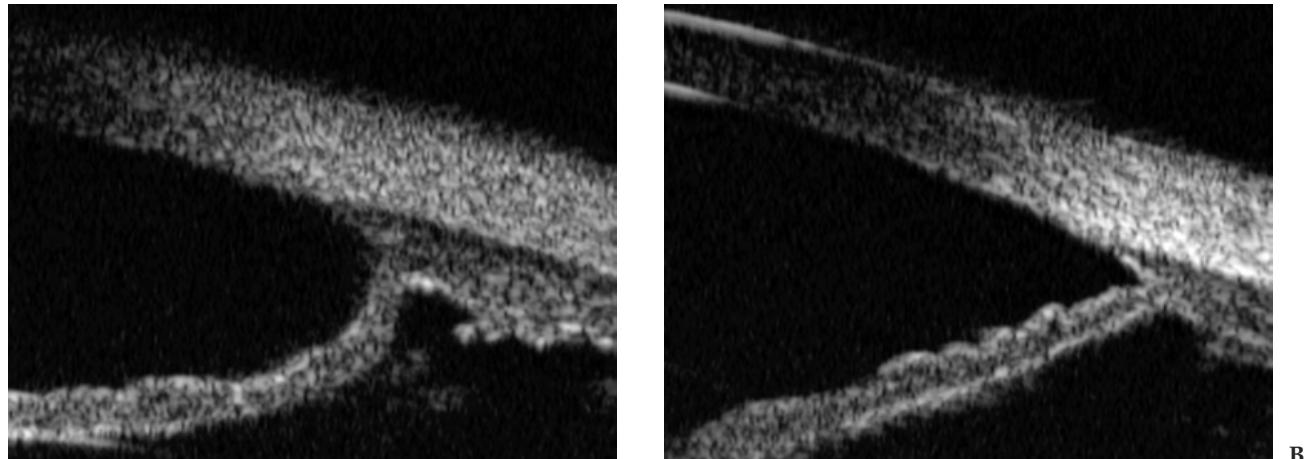


FIGURE 19-8 High-frequency ultrasound of a patient with recurrent, severe episodes of elevated intraocular pressure (IOP), blurred vision, and halos following exercise. Despite marked, preoperative concavity (A), the iris returned to a neutral position after laser iridotomy (B), and IOP spikes diminished.

this treatment may be best reserved for patients with early nerve damage and severe, intermittent episodes of elevated IOP unresponsive to medication.

CONTROVERSY

Laser iridotomy may help prevent reverse pupillary block. Because it can take many years to assess the effectiveness of the iridotomy, no controlled study has yet proven that it prevents the continued release of iris pigment epithelium.

GLAUCOMA THERAPY

Once pigmentary glaucoma is established, or the IOP in a pigment dispersion syndrome patient reaches a level high enough to damage the optic nerve, one should initiate treatment to lower the IOP. This therapy closely resembles the management of primary open-angle glaucoma, with a stepwise progression from medical to laser therapy and then to incisional surgery, if needed.

Initial treatment consists of a simple topical regimen, usually a topical beta-blocker, if not contraindicated, once or twice daily to the more severely affected eye, followed by bilateral therapy if this lowers the pressure adequately. Other medications can be tried if this fails to lower IOP, or added to the existing regimen if the initial response is significant, but not to the desired level. These include alpha agonists and topical carbonic anhydrase inhibitors two or three times daily. Although limited by the above-mentioned side effects of induced myopia and possible retinal detachment, miotics specifically increase outflow through the trabecular meshwork and are very effective pressure-lowering agents in pigmentary glaucoma. Occasionally, oral carbonic anhydrase inhibitors are necessary

when topical agents are ineffective or not tolerated. Topical prostaglandin can also be used to lower IOP in this condition. It has the advantages of relatively few ocular and systemic side effects and once-daily application.

Argon laser trabeculoplasty (ALT) is an effective treatment for open-angle glaucoma.²⁸ Among secondary forms of glaucoma, it is most successful in patients with pigmentary glaucoma, pseudoexfoliation glaucoma, and angle-closure glaucoma after iridotomy.²⁹ Although ALT successfully lowers IOP in pigmentary glaucoma patients initially, this effect wanes faster than in patients with primary open-angle glaucoma.³⁰ One study showed that the success rates of ALT treatment for pigmentary glaucoma were 80, 62, and 45% at 1, 2, and 3 years after treatment.³¹ Success rates in patients under age 42 were 72% after 5 years. Because of the heavily pigmented trabecular meshwork, standard ALT power settings may cause overtreatment and permanent damage to the meshwork. Initial power settings should be reduced from normal and then gradually adjusted as needed to produce a slight blanching of the anterior trabecular meshwork with each application.

In general, medical treatment controls IOP less successfully in pigmentary glaucoma patients (66%) than in primary open-angle glaucoma patients (85%).⁴ When glaucoma medications and ALT fail to achieve the target pressure, patients with pigmentary glaucoma require glaucoma filtering surgery. Compared with primary open-angle glaucoma patients, Scheie reported that pigmentary glaucoma patients required surgery nearly 15 years earlier, and needed more surgical procedures to attain adequate IOP control.⁴ Nevertheless, fewer pigmentary glaucoma patients suffer visual field loss if treated surgically (25%) than if treated medically (38%).⁸

The surgical techniques for treating pigmentary glaucoma are similar to that for primary open-angle glaucoma. Myopic patients tend to develop hypotony maculopathy more often than non-myopic patients. The surgeon should

try to avoid the development of postoperative hypotony in these patients with slight modifications in surgical techniques. This may include fashioning a slightly thicker trabeculectomy flap, securing it with extra sutures, and limiting the use of intraoperative antimetabolites both during and after surgery.

Although pigmentary glaucoma may be more aggressive than primary open-angle glaucoma, requiring more medical therapy and earlier surgical intervention, the long-term prognosis of pigmentary glaucoma is generally good. Irreversible vision loss secondary to progression of scotomata develops in relatively few eyes.⁸

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PSEUDOEXFOLIATION SYNDROME AND GLAUCOMA

Douglas H. Johnson, M.D.

Pseudoexfoliation syndrome is characterized by the development of white, dandruff-like flakes on the lens, pupillary margin, and other anterior segment structures in older patients. Pseudoexfoliation material has recently been found in sites other than the eye, and may be a diffuse basement membrane disease, or represent a generalized form of elastosis. Although the condition appears most frequently in patients with Scandinavian heritage, it occurs in almost all races and in all climates. In the United States, up to 28% of patients with open-angle glaucoma are found to have pseudoexfoliation syndrome, whereas in the Nordic countries this may be as high as 47%.¹⁻⁵

Over time, nearly one half of all patients with pseudoexfoliation will have glaucoma, and, of patients with pseudoexfoliation syndrome and no glaucoma at the initial examination, 15% will develop elevated pressure after 10 years.⁵⁻¹⁰ Pseudoexfoliation glaucoma is more difficult to control than primary open-angle glaucoma, with higher intraocular pressures and a poorer response to medication. In addition, pseudoexfoliation may cause weakened zonules and poorly dilating pupils, predisposing the eye to complications during cataract surgery. Although no systemic disease is associated with pseudoexfoliation, the diagnosis of the condition by careful biomicroscopy should alert the clinician to the potential for glaucoma both at the initial examination and in the future, as well as for difficulties in cataract surgery.

BACKGROUND

Pseudoexfoliation syndrome was first described in patients from Finland, in whom it was noted in almost half of the patients with glaucoma.¹¹ Initially thought to be an exfoliation or delamination of the lens capsule, as seen in glassblowers, several theories later arose as to the

origin of the material. Some researchers felt that pseudoexfoliation was an abnormal precipitation of material upon the lens capsule, rather than an abnormality of the capsule itself, and termed it *pseudoexfoliation*.^{12,13} Recent studies have again pointed to the lens capsule as one source of the material, and have also found it in a variety of ocular and extraocular sites.^{2,14-26} Opinions on the exact terminology for the condition remain mixed, prompting a variety of other names, including senile pseudoexfoliation of the lens capsule, senile uveal pseudoexfoliation, fibrillopathia epitheliocapsularis, the basement membrane pseudoexfoliation syndrome, and glaucoma capsulare.^{14-18,27-29}

PEARL... Pseudoexfoliation glaucoma = exfoliation glaucoma = glaucoma capsulare. Although the terminology for this condition has varied in the past, most authors now use the term pseudoexfoliation glaucoma.

EPIDEMIOLOGY

Numerous studies report high prevalence rates from Nordic countries, but this syndrome has also been described in most other peoples of the world.³⁰ Prevalence rates vary not only among races, but also depending upon examination techniques. These include pupillary dilation, the examiner's experience level, population age, and whether the data are collected prospectively or retrospectively. Prospective studies using pupil dilation are most likely to detect this condition because its early manifestations may be subtle.

Pseudoexfoliation is common in Finland, where prevalence is 20%, and Norway,^{30,31} but less common in Denmark, Austria, and Switzerland, where the prevalence is 2% in each country.^{30,32} It has been reported in 10% of

blacks with glaucoma in South Africa,³³ yet in only 0.4% of blacks in Louisiana,³⁴ whose ancestral homes were mainly West Africa. Rates in other populations tend to be similar or lower: 4.4% in Peruvian Indians, 2% in India,³⁰ 1.8% in Massachusetts,³⁵ and 0.2% in Japanese.³⁰

Currently, no studies have identified a specific inheritance pattern for pseudoexfoliation. This may be due to its onset late in life, when a patient's parents have died and before their children are old enough to develop the condition.

Pseudoexfoliation syndrome is more common after age 50, and nearly doubles in incidence with each successive decade.^{1,30,31,35-37} Forsius reported a prevalence of 10% among Finns age 50 to 69 years and 25.3% among Finns age 70+ years.³⁰ The Framingham study found a 0.6% prevalence for people age 52 to 64, rising to 5.0% by age 75 to 85.³⁴ In the few cases occurring in patients under age 40, all eyes had undergone prior intraocular surgery or trauma.³⁸

The high prevalence rates in Nordic countries might suggest that northern latitudes, cold air, hours of sunlight, or some other climate-related factor contributes to producing the pseudoexfoliation syndrome. However, no strong evidence for this exists. This syndrome is common in Laplanders but rare in Eskimos, who live at similar latitudes.³⁰ It is also common in Saudi Arabia (13.2%),³⁷ which has a different climate with more intense sunlight than the northern latitudes. Attempts to connect pseudoexfoliation with ultraviolet light exposure have been mixed, and this condition is not correlated with clinical signs characteristically associated with ultraviolet exposure, such as pterygia, climatic keratopathy, or cataract.³⁰

Pseudoexfoliation syndrome appears unilateral in about 50% of patients at the time of diagnosis.^{2,3,6,35} Because most theories of pathogenesis suggest a metabolic or degenerative cause, which should occur bilaterally, pseudoexfoliation may be a bilateral process with an asymmetric presentation. This is supported by the observations that, in clinically diagnosed unilateral pseudoexfoliation syndrome, up to 76% of uninvolved fellow eyes can have exfoliative material on their ciliary processes,³⁹ and histologic evidence of pseudoexfoliation can appear at autopsy in many clinically "normal" fellow eyes.^{40,41} In addition, patients with unilateral pseudoexfoliation syndrome often develop it in the fellow eye after 5 to 10 years. In one study, up to 43% eventually became bilateral.^{3,4,6,42}

SPECIAL CONSIDERATION

How could a presumed systemic or genetic condition be unilateral? Although pseudoexfoliation syndrome may present unilaterally, most studies agree it is a bilateral condition with an asymmetric presentation.

PATHOGENESIS

Pseudoexfoliation material appears in many regions of the ocular anterior segment, as well as outside the eye, supporting the possibility that this is a generalized metabolic condition. Although the exact nature of the pseudoexfoliation material is currently unknown, it appears to play a prominent role in obstructing aqueous humor outflow and causing glaucoma.

PATHOLOGY

Intraocular Pathology

Pseudoexfoliation material arises in a variety of sites within the eye. Clinicians are most likely to see it on the anterior lens capsule, where it occurs in several regions, forming a central disc, an intermediate clear zone, and a peripheral granular zone (Fig. 20–1A–C).¹⁴⁻¹⁸ The posterior capsule does not appear involved, whereas the material seems to arise from the equator.¹⁴⁻¹⁸ Of interest, pseudoexfoliation material can appear on the vitreous face and anterior surface of intraocular lenses, often 5 or more years after cataract surgery.⁴³ This suggests that the material is not produced by the anterior capsule, but gets deposited there from the aqueous humor.¹²

Pseudoexfoliation also arises from the basement membrane region of the ciliary processes. Ultrastructurally, the material coats the ciliary processes and appears intermixed with a multilaminar basement membrane,^{13,17,18,44-48} whereas the zonules themselves appear intact. Accumulation of pseudoexfoliation material at the insertion of the zonular fibers into the ciliary body may weaken this attachment, leading to zonular rupture and lens dislocation.^{47,48}

In the iris, pseudoexfoliation material can appear in the iris pigment epithelium and blood vessel walls and on the anterior stroma.^{18,49,50} Clinically, it can be especially prominent on the pupillary margin. Microscopically, exfoliative material is intermixed with a duplicated and disorganized basement membrane of the iris pigment epithelial cells, which also show degeneration and disruption. The iris vasculature may contain subendothelial accumulations of material, often in conjunction with disrupted basement membranes.^{18,49,50} These changes may occlude the lumen in some areas, and produce dropout and leakage of iris vessels as seen with fluorescein angiography.^{51,52}

In the trabecular meshwork, pseudoexfoliation material appears in the aqueous channels of the uveal meshwork, the intertrabecular spaces, juxtaganular tissue, and Schlemm's canal (Fig. 20–2A,B).^{13,40,53-56} These locations suggest deposition of material from the aqueous, although some, but not all, studies suggest that trabecular cells can produce this material directly.^{40,53-56} In advanced cases with glaucoma, the pseudoexfoliation material appears to disrupt Schlemm's canal, causing it to fill with fibrous tissue and occlude the lumen of the

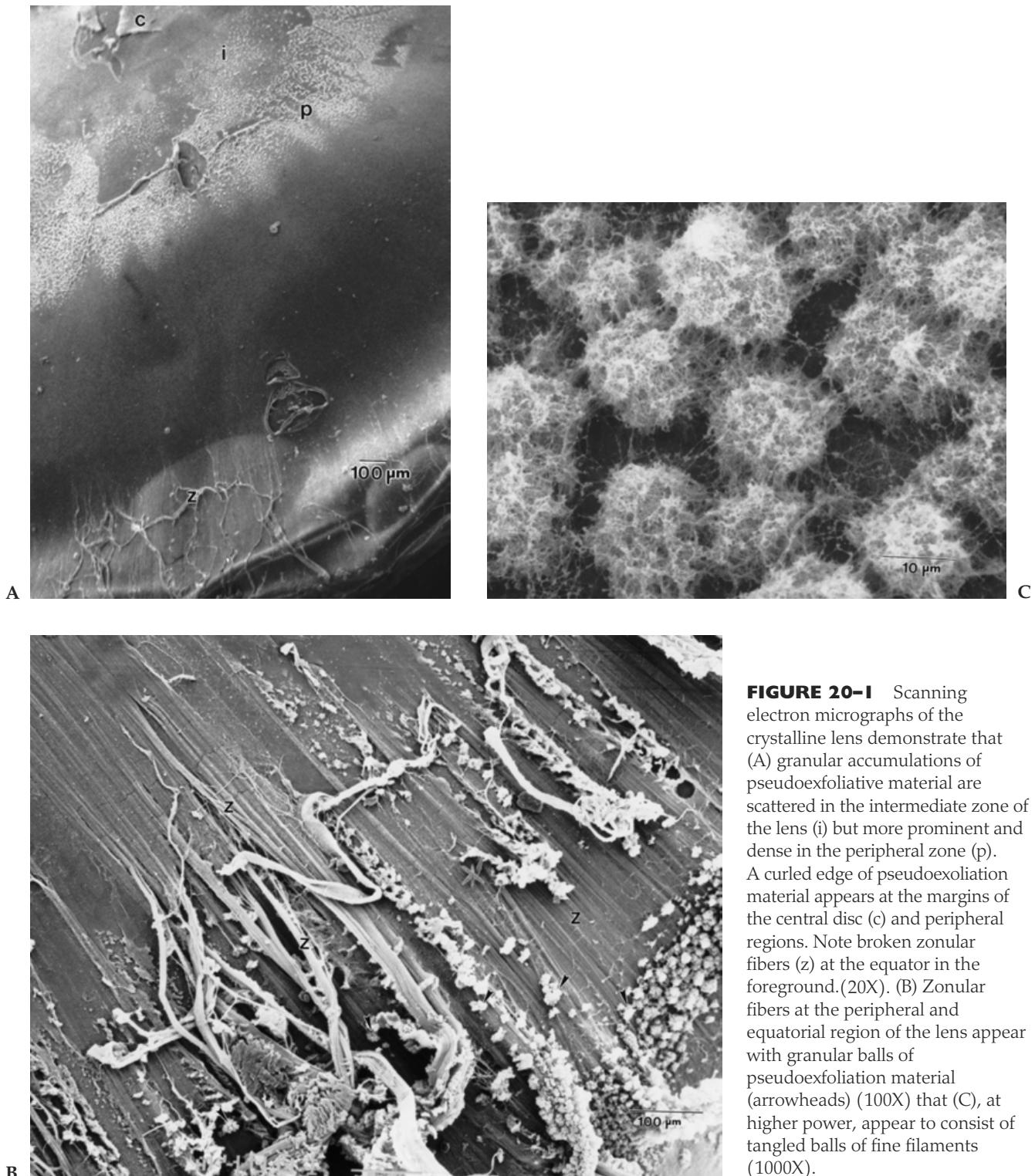


FIGURE 20-1 Scanning electron micrographs of the crystalline lens demonstrate that (A) granular accumulations of pseudoexfoliative material are scattered in the intermediate zone of the lens (i) but more prominent and dense in the peripheral zone (p). A curled edge of pseudoexfoliative material appears at the margins of the central disc (c) and peripheral regions. Note broken zonular fibers (z) at the equator in the foreground. (20X). (B) Zonular fibers at the peripheral and equatorial region of the lens appear with granular balls of pseudoexfoliation material (arrowheads) (100X) that (C), at higher power, appear to consist of tangled balls of fine filaments (1000X).

canal.⁵⁵ Eyes with pseudoexfoliation syndrome also have increased meshwork pigmentation, which probably arises from peripupillary iris pigment epithelium rubbing on the lens capsule and undoubtedly washes in from the aqueous. This appears as granules within trabecular cells and in the inter trabecular spaces.

Extraocular Pathology

Pseudoexfoliation material has been found in both the bulbar and the palpebral conjunctiva,^{2,19-24} where it is associated with both stromal and vascular elastic fibers.^{21,23,24} Streeten et al. reported an intermingling of the pseudoexfoliation fibrils with elastic fibrils and suggested

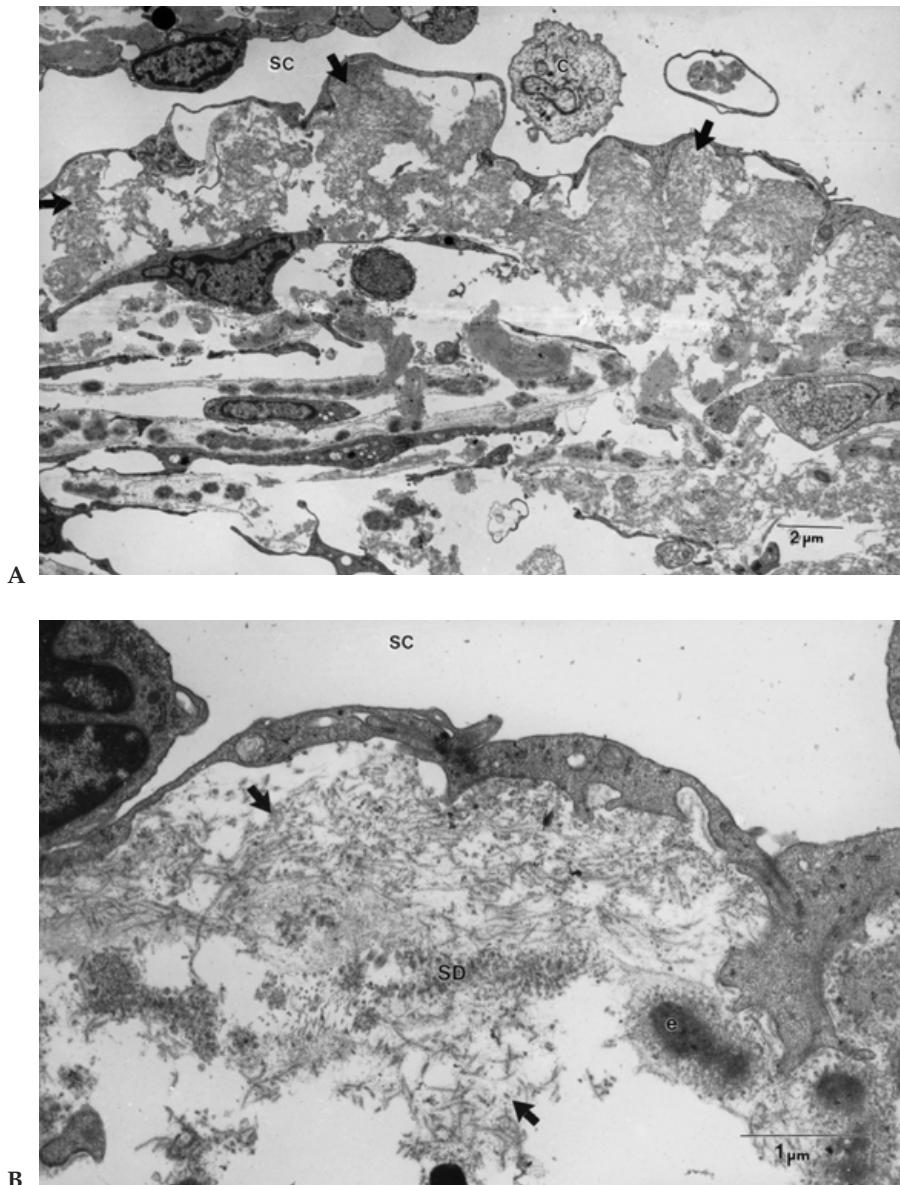


FIGURE 20-2 Transmission electron micrographs of the trabecular meshwork from an eye with pseudoexfoliation glaucoma demonstrate (A) clumps of pseudoexfoliative material (arrows) directly beneath the inner wall of Schlemm's canal (SC). A wandering cell (C) has entered the canal (6250X). (B) Higher-power view adjacent to an endothelial cell in the inner wall of Schlemm's canal (SC) confirms that the material is a tangle of randomly arranged, fine filaments and thicker fibrils (arrows). e, elastic tendon; SD, tendon sheath (50,000X).

that the pseudoexfoliation syndrome may be a type of elastosis, resulting from an abnormal aggregation of components related to elastic microfibrils.²¹

Several studies have found pseudoexfoliation material in sites distant from the eye, including skin from the eyelid, buttocks, and behind the ear.^{25,26,56-59} Here, too, it demonstrated a predilection for elastic fibers and appeared influenced by an accompanying dermal elastosis.^{25,26,57} Additional extraocular sites consist of the connective tissue of the heart, lungs, liver, gallbladder, kidney, and cerebral meninges.^{23,26,57,58} The lamina cribrosa of the optic disc appears to undergo elastosis to a greater extent than would be expected by intraocular pressure effects alone, although pseudoexfoliation material has not been identified in this region.⁶⁰

Despite the microscopic appearance of pseudoexfoliative material in these other tissues, patients do not have

an increased mortality rate, although one study reported an association of pseudoexfoliation with vascular disease, including histories of angina, hypertension, or stroke.⁶¹

COMPOSITION OF PSEUDOEXFOLIATION MATERIAL

Many enzymatic, histochemical, and immunologic tests have been performed on pseudoexfoliative material.^{18,62-70} Under transmission electron microscopy, it appears as a tangle of filaments and fibrils embedded in an amorphous ground substance thought to consist of proteoglycans (Figs. 20-2A,B,20-1A-C)⁶²⁻⁷⁰ The small filaments appear similar to elastic microfibrils, and the larger thick fibrils resemble aggregations of the small filaments.²¹ Light microscopy and lectin staining concur that proteoglycans are probably present in pseudoexfoliation material.

CONTROVERSY

The nature and origin of pseudoexfoliation material are currently in dispute. Some contend that this material is related to abnormal production of basement membranes, whereas other evidence suggests that it results from elastic fiber degeneration.

Current theories suggest that pseudoexfoliation material may arise either from abnormal basement membrane, or from a degeneration of the elastic fiber system.^{18,25,29,59,65,68} Basement membranes are a mixture of material secreted by epithelial cells throughout the body. In addition to its association with duplicated, disrupted, or degenerated basement membranes, pseudoexfoliation material labels with antibodies directed against several components of basement membranes, including laminin, fibronectin, elastin, and the proteoglycans heparan sulfate and chondroitin sulfate.⁶⁸ Naumann and colleagues concluded that pseudoexfoliation material is a “multi-component expression of a disordered extracellular matrix synthesis, including the incorporation of the principal noncollagenous basement membrane components.”⁶⁸

Elastic tissue consists of a central core of an amorphous, insoluble protein (elastin), surrounded by microfibrils.^{71,72} Streeten has demonstrated that elastin, tropoelastin, and fibrillin are all present in pseudoexfoliation material.^{25–27} In addition, pseudoexfoliation material shares light microscopic staining characteristics with zonular fibers, which are similar in amino acid composition and structure to microfibrils of elastin.^{25,73,74}

Pseudoexfoliation material is intimately related to areas of elastosis throughout the body, and Streeten and colleagues consider pseudoexfoliation to be a type of elastosis,²¹ a form of elastic tissue degeneration, in which they have also noted pseudoexfoliation material arising from fibroblasts and other local cells.²¹ They have also commented, however, that pseudoexfoliation material may be a product of local basement membrane-secreting cells.⁷¹

PATHOGENESIS OF PSEUDOEXFOLIATION GLAUCOMA

Histologic evidence suggests that this form of glaucoma is secondary to accumulation of pseudoexfoliation material within the trabecular meshwork (see Fig. 20–2A,B).⁴⁰ In a study of 19 autopsy eyes, maximum intraocular pressure measured clinically during life and average intraocular pressure while on treatment were both related to the amount of material within the juxtaganular region of the trabecular meshwork.⁴⁰ In most cases of glaucoma the trabecular meshwork appeared otherwise intact. However, advanced cases demonstrated disorganization of the

juxtaganular region and a decrease in the size of Schlemm's canal.^{40,54,55} Ultrastructurally, the trabecular meshwork from eyes with pseudoexfoliation glaucoma differ from those with primary open-angle glaucoma, and lack the excess tendon sheath material found in advanced cases of primary open-angle glaucoma.⁷⁵

The heavy pigmentation of the meshwork seen on clinical gonioscopy may also contribute to the development of pseudoexfoliative glaucoma, and some investigators have suggested a relationship between the amount of pigment seen with gonioscopy and the incidence of glaucoma.^{3,24,76} Histologically, pigment is present within trabecular cells and occasionally within the intertrabecular spaces. However, these changes do not appear to narrow the outflow spaces enough to produce elevated pressure.^{39,54}

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Patients with pseudoexfoliation glaucoma have few symptoms unless they develop advanced glaucomatous visual field loss (Table 20–1).

The most characteristic anterior segment signs of pseudoexfoliation syndrome are the whitish granular deposits and dandruff-like flakes of pseudoexfoliation material on the anterior capsule of the crystalline lens (Fig. 20–3A–E). The pattern of deposition resembles a target, with a central disc of gray material surrounded by a clear zone and then an outer peripheral zone of pseudoexfoliative material. Movements of the pupil probably cause this targetlike appearance: the central disc is the approximate size of the pupil at its smallest diameter, whereas the intermediate clear zone results from the pupillary border rubbing pseudoexfoliative material off the lens. A similar pattern can also appear on the anterior surface of intraocular lenses.⁴³ Variations of this appearance include the lack of a central disc, streaks of pseudoexfoliative material in the intermediate clear zone, and material appearing as a partially detached sheet, resembling delamination of the anterior capsule.

Dilation of the pupil is required to detect all possible cases of pseudoexfoliation syndrome because the homogeneous pseudoexfoliative material in the central disc may be extremely subtle and the intermediate clear zone and peripheral zone lie well outside the undilated pupil. Up to 20% of pseudoexfoliative cases are missed if examined with undilated pupils.³⁰ Flakes of pseudoexfoliative material may also appear on the corneal endothelium, the zonular fibers, ciliary processes, intraocular lenses, and anterior vitreous face, and in the trabecular meshwork (Fig. 20–4A–E).

The pupillary margin may provide clues to the presence of pseudoexfoliation even without dilation. Pseudoexfoliation material, ranging in appearance from flakes to a fine deposit, often clings to the pupillary ruff, which can also develop a pigmentary atrophy along with a

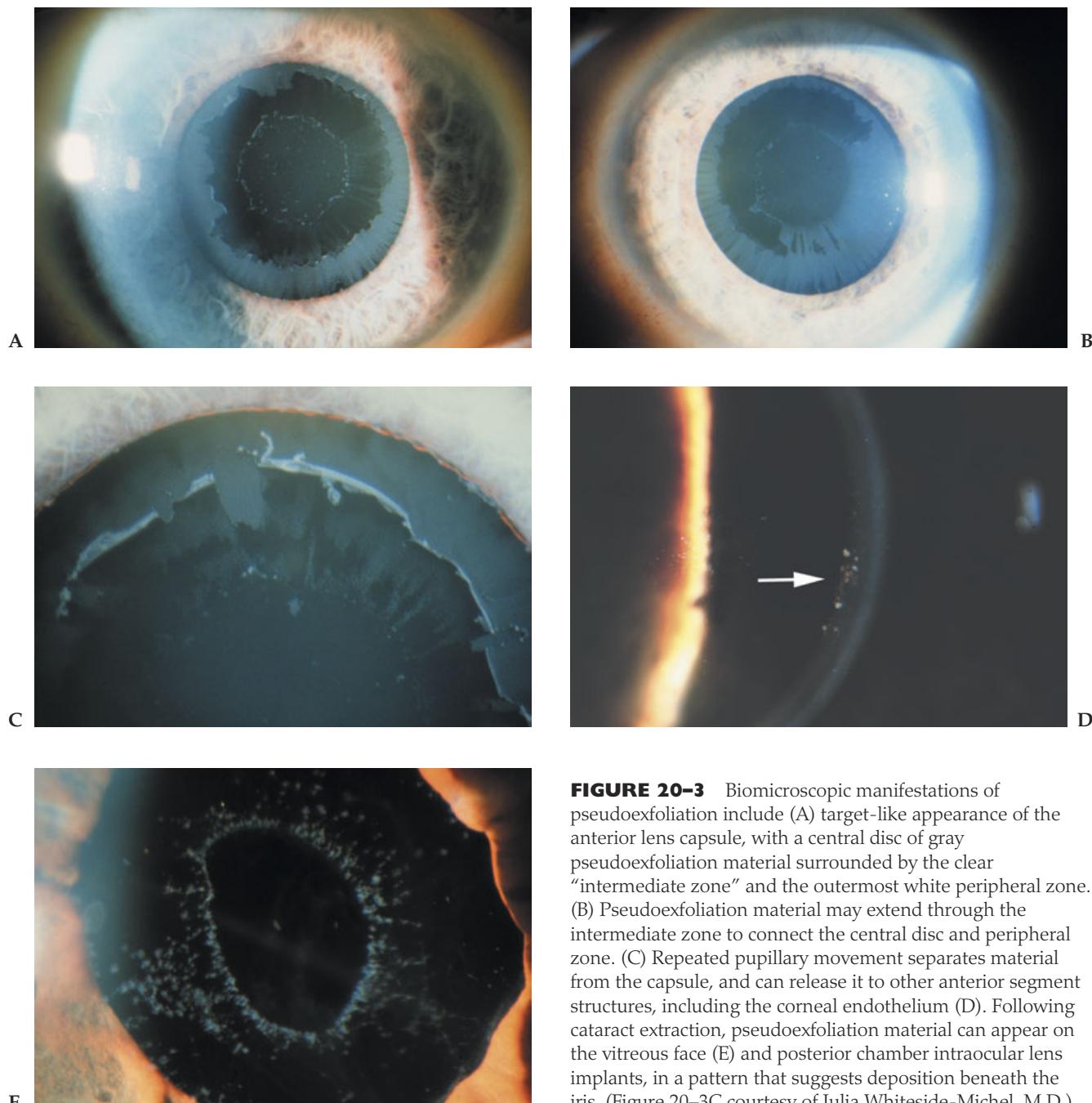


FIGURE 20-3 Biomicroscopic manifestations of pseudoexfoliation include (A) target-like appearance of the anterior lens capsule, with a central disc of gray pseudoexfoliation material surrounded by the clear “intermediate zone” and the outermost white peripheral zone. (B) Pseudoexfoliation material may extend through the intermediate zone to connect the central disc and peripheral zone. (C) Repeated pupillary movement separates material from the capsule, and can release it to other anterior segment structures, including the corneal endothelium (D). Following cataract extraction, pseudoexfoliation material can appear on the vitreous face (E) and posterior chamber intraocular lens implants, in a pattern that suggests deposition beneath the iris. (Figure 20-3C courtesy of Julia Whiteside-Michel, M.D.)

TABLE 20-1 DIAGNOSIS OF PSEUDOEXFOLIATION

Symptoms	None until extensive visual field loss
Signs	White material and flakes on anterior lens capsule, pupillary margin, zonules, corneal endothelium, and trabecular meshwork Patchy to confluent peripupillary iris transillumination defects Loss of pigment ruff from pupillary border Moderate to dense segmental pigmentation of the trabecular meshwork Limited pupillary dilation Phacodonesis and iridodonesis Zonular rupture during cataract surgery Elevated intraocular pressure Glaucomatous optic nerve damage and visual field defects



FIGURE 20-4 (A) Close inspection of the pupillary margin often reveals fine white deposits and flakes, which can often be extremely subtle along with absence of the pupillary ruff. (B) Retroillumination may show patchy, peripupillary, and midperipheral transillumination defects that are often confluent and differ from the slitlike, radial defects of pigmentary glaucoma. (C) Gonioscopy often demonstrates increased, patchy pigmentation of the trabecular meshwork, which in this case has overlying flakes of pseudoexfoliation material. (D) Involvement of the zonules may lead to lens subluxation or complications during cataract surgery. (E) Pseudoexfoliative material on the ciliary processes and zonules is generally most apparent in postmortem or enucleated specimens. (Figure 20-4D courtesy of Julia Whiteside-Michel, M.D.; Figure 20-4E courtesy of W. Richard Green, M.D.)

patchy, "moth-eaten" peripupillary iris transillumination that results from constant rubbing of the iris on the anterior lens capsule (Fig. 20-4A,B).

Gonioscopy often reveals moderate to dense segmental pigmentation of the trabecular meshwork and the inferior Schwalbe's line. Although this pigmentation is characteristically dark brown or black, it is not as dense or homogeneous as that seen in pigmentary glaucoma (Fig. 20-4C).

Characteristic glaucomatous optic nerve damage with generalized or focal neuroretinal rim erosion and characteristic visual field defects may be present on diagnosis, or may develop over time. The extent of this injury gener-

ally correlates with the degree and duration of the pressure elevation.

Although several studies comment on finding gonioscopically narrow angles in eyes with pseudoexfoliation syndrome, none have documented an increase in the incidence of acute angle closure attacks.⁷⁷⁻⁸⁰ However, weakened or ruptured zonular fibers could allow lens subluxation, resulting in secondary angle closure, or acute angle closure from pupillary block (Fig. 20-4D).

At the time of discovery, 6 to 24% of patients with pseudoexfoliation have either glaucoma or elevated intraocular pressure.^{6,37,81,82} Approximately 50% of patients with

pseudoexfoliation syndrome will ultimately be diagnosed with glaucoma, either during the initial examination or at a later time, with reports ranging from 20 to 85%.^{3,6,75,81,83}

PEARL... Beware of glaucoma at the time of discovery of pseudoexfoliation syndrome. Initial examination should always include careful optic disc evaluation, and visual field testing and diurnal intraocular pressure measurement in cases with suspicious discs or intraocular pressures.

DIFFERENTIAL DIAGNOSIS

Few things are easily confused with pseudoexfoliation syndrome (Table 20–2). Many patients diagnosed with open-angle glaucoma actually have pseudoexfoliation syndrome with glaucoma. Surveys of patients with established open-angle glaucoma indicate that between 3 and 47% of these open-angle glaucoma cases are pseudoexfoliation glaucoma, with figures in the United States ranging up to 28%.^{1–5,84} These percentages probably increase with advancing age.

All patients with primary open-angle glaucoma should be carefully examined for evidence of subtle pseudoexfoliation, particularly after dilation. Distinguishing pseudoexfoliative glaucoma from primary open-angle glaucoma has direct clinical importance. Aside from their increased potential for complications during cataract surgery, intraocular pressure in eyes with pseudoexfoliation glaucoma is generally more unpredictable and refractory to medical therapy than in eyes with primary open-angle glaucoma.

In pigmentary glaucoma, the trabecular pigmentation is dense, even, and dark brown or black compared to the irregular, more segmental pigmentation of pseudoexfoliation. The iris transillumination defects of pigmentary glaucoma are elongated radial spokes in the periphery of the iris, whereas those of pseudoexfoliation syndrome appear as moth-eaten patches around the pupil, often with some loss of the pupillary ruff.²⁴ Although uveitis may produce synechiae, fibrin, or cyclitic membranes that involve the anterior lens capsule with whitish debris, this lacks the homogeneous granular appearance and characteristic flakes of exfoliative material.

MANAGEMENT

GLAUCOMA

Pseudoexfoliation syndrome can be a risk factor for the development of glaucoma. In patients with pseudoexfoliation syndrome and no glaucoma at the initial examination, 5% will develop an elevated intraocular pressure or glaucoma after 5 years, and 15% after 10 years (reports range from 5 to 34% at 5 years).^{6–10} Patients with pseudoexfoliation syndrome must be examined at regular intervals, always including careful study of the optic disc. Suspicious optic nerves or pressures should prompt re-evaluation in several months, with visual field testing and optic disc photographs as needed.

A patient with pseudoexfoliation syndrome and normal discs and pressures should have regular, periodic examinations at least every 1 to 2 years, with initial baseline optic disc drawings or photographs. Glaucoma, once diagnosed, requires standard medical treatment along with examinations every 3 to 6 months because intraocular pressure often becomes more difficult to control with time.

PEARL... Beware the development of glaucoma in pseudoexfoliation syndrome. Because half of patients may ultimately have glaucoma, patients with pseudoexfoliation and no glaucoma should be examined at least every 1 to 2 years.

Laser trabeculoplasty is especially effective in pseudoexfoliation glaucoma, with reported initial success rates up to 80%.^{85,86} These increased success rates may result from the higher prelaser intraocular pressures and generally increased trabecular pigmentation in these patients.

However, as in primary open-angle glaucoma, success rates decrease with time, averaging 50% or less by 5 years. Although mixed, most reports suggest that retreatment with laser is less successful than the initial treatment.⁸⁶

Numerous studies have commented on the failure of long-term medical treatment and late failures of laser trabeculoplasty^{85,87–89} in pseudoexfoliative glaucoma. In one, 61% of patients had undergone either laser trabeculoplasty (35%) or glaucoma surgery (26%) by the time they

TABLE 20–2 DIFFERENTIAL DIAGNOSIS OF PSEUDOEXFOLIATION GLAUCOMA

Condition	Differentiating Features
Primary open-angle glaucoma	Lack of pseudoexfoliation material within the anterior segment Lack of increased, or patchy trabecular meshwork pigmentation
Pigmentary glaucoma	Kruckenberg spindle Lack of pseudoexfoliation material Radial, midperipheral iris transillumination defects Heavier, more confluent trabecular meshwork pigmentation Pigment on iris, lens equator, and zonules
Uveitis	Fibrin, cyclitic membrane less homogeneous than true pseudoexfoliation material Irregular, lighter trabecular meshwork pigmentation

died.⁸⁷ In this same group of patients, 25% became blind in at least one eye, and 8% in both eyes. Both eyes became blind in 15% of patients with bilateral pseudoexfoliative glaucoma.

In patients who do not respond to medications or laser, routine filtration surgery can achieve success rates similar to those of surgery in patients with primary open-angle glaucoma.⁸⁵

CATARACT SURGERY

Weakened attachments of the zonular fibers to the ciliary body can cause subluxation of the crystalline lens in pseudoexfoliation syndrome.⁴⁸ This, plus poor pupillary dilation, also predisposes these eyes to surgical complications during cataract surgery, with a five- to ten-fold increase in the rate of zonular breaks, capsular dialysis, or vitreous loss.^{90–93} Zonular ruptures and displacement of the posterior capsule may occur even with a gentle, atraumatic surgical technique.

Surgeons should anticipate weakened zonules during cataract surgery on patients with pseudoexfoliation syndrome. Preoperative signs may range from lens dislocation to the more subtle iridodonesis or phacodonesis. The examiner can elicit these latter signs during slit-lamp examination by asking the patient to move the eye briefly, and should routinely check for this on all patients before cataract surgery. Problems encountered during surgery on one eye are a clear warning of potential problems in the unoperated fellow eye.

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NEOVASCULAR GLAUCOMA

John C. Morrison, M.D. and Michael L. Klein, M.D.

Neovascular glaucoma (NVG) is a severe form of glaucoma, usually associated with posterior segment eye disease, in which abnormal, new blood vessels obstruct aqueous humor outflow. When fully developed, NVG presents with characteristic iris neovascularization, a closed anterior chamber angle, and highly elevated intraocular pressure (IOP). Early detection of the neovascularization and its causes, however, can prevent angle closure and the need for surgery. Better understanding of the pathogenesis of neovascularization has led to effective prevention and improved surgical management, when necessary.

BACKGROUND

Our understanding of NVG began in 1906, with the histologic finding of new blood vessels on the iris of patients with central retinal vein occlusion (CRVO), and, later, in patients with diabetes.^{1,2} Subsequent correlation of gonioscopically visible anterior chamber angle vessels with histologic evidence of connective tissue and peripheral anterior synechiae suggested that this tissue produces glaucoma by obstructing aqueous outflow through the trabecular meshwork.³ The term *neovascular glaucoma* was introduced in 1963⁴ and has gradually supplanted older terms, such as *rubeotic* and *hemorrhagic* glaucoma. Effective approaches to preventing neovascularization and managing this form of glaucoma have evolved rapidly over the past two decades.

PATHOGENESIS

PATHOLOGY

The major histopathologic findings in the anterior segment consist of new blood vessels associated with a fibrous membrane. The vessels themselves lack adventitia and usually occur on the iris surface. Ultrastructurally, their endothelial cells appear fenestrated and lack tight intercel-

lular junctions with their neighbors, encouraging vascular leakage and variable amounts of cellular inflammation.⁵

The fibrous membrane typically overlies the new blood vessels and contains fibroblasts with smooth muscle characteristics (myofibroblasts). Contraction of these myofibroblasts produces many of the iris and anterior chamber abnormalities that characterize NVG.⁶

Fine tufts of new vessels, originating from iris arterioles, usually appear first at the pupillary margin, and then spread into and over the iris. Although new vessels in the angle may arise from ciliary body arterioles, most extend from the iris neovascularization. Once in the anterior chamber angle, these vessels cross the scleral spur, spreading over and invading the trabecular meshwork.⁷

By covering the meshwork, the fibrovascular membrane can obstruct aqueous outflow, even though the anterior chamber angle may appear open. Contraction of this membrane by myofibroblasts produces peripheral anterior synechiae, angle closure (Fig. 21-1), and pupillary distortion. In advanced cases, this produces a "pseudo-angle," which can be covered by endothelium.⁸

PREDISPOSING CONDITIONS

CRVO and diabetes mellitus produce nearly two thirds of all cases of NVG. Carotid artery occlusion, followed by numerous other, much less common, conditions accounts for the remainder of the causes. Most of these conditions involve retinal ischemia, along with other potential mechanisms, as noted in Table 21-1.

Central Retinal Vein Occlusion

Several studies report a wide range in the incidence of glaucoma following CRVO, with 16% for the Central Vein Occlusion Study (CVOS)⁹ and an overall average of 30%.¹⁰ The recognition that retinal ischemia encourages iris neovascularization greatly improved predicting which

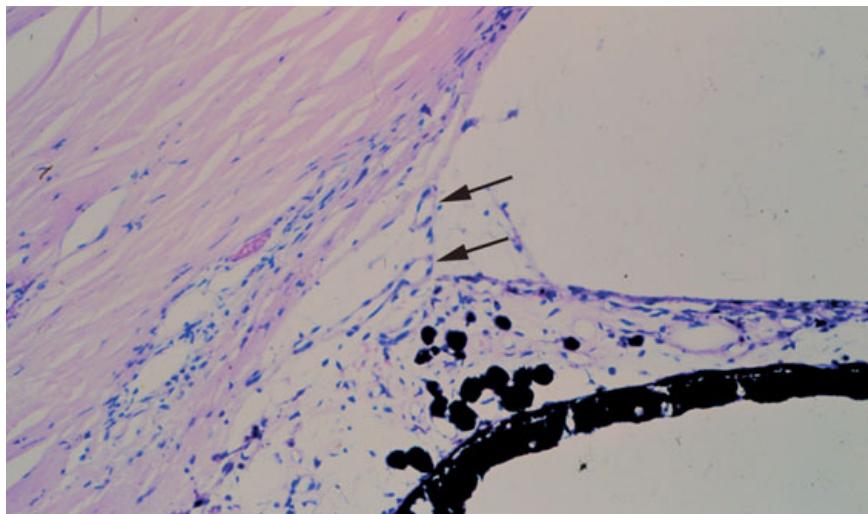


FIGURE 21-1 Histopathology of neovascular glaucoma illustrates a fibrovascular membrane that obliterates the anterior border layer of the iris and gives it a smooth, flat surface. Neovascular capillaries (arrows) bridge the anterior chamber angle to the trabecular meshwork, producing a peripheral anterior synechia. Note capillary within Schlemm's canal filled with erythrocytes.
(Courtesy of W. Richard Green, M.D.)

patients would develop NVG. Hayreh first made this distinction,¹¹ classifying eyes as having either “venous stasis” (not to be confused with venous congestion following carotid occlusion), which had a low incidence of NVG, or “hemorrhagic” retinopathy, in which NVG was much more likely. Now, these conditions are more commonly termed nonischemic and ischemic CRVO.

In general, the occurrence of iris neovascularization requires ischemia of at least half of the retina.¹² The association of NVG with retinal ischemia, as documented by fluorescein angiography, can be as high as 60%,¹³ depending on the degree and the definition of nonperfusion. Although many cases of NVG occur within 3 months of the CRVO, over 80% appear within the first 6 months,¹² and glaucoma develops earliest in eyes with the most extensive ischemia.

Unfortunately, an initial demonstration of retinal perfusion does not eliminate the possibility of developing NVG. Intraretinal hemorrhages can obscure the fluorescein

capillary pattern in 10 to 30% of cases. In addition, a significant number of eyes initially demonstrating perfusion can convert to retinal ischemia, defined as greater than 10 disc diameters, with as many as one third converting over the 3 years of the CVOS.⁹

Currently, the presenting visual acuity is the most reliable predictor of NVG following CRVO, correlating closely with both retinal nonperfusion and anterior segment neovascularization (Table 21-2). In the CVOS, over 30% of eyes with acuity less than 20/200 within 1 month of the occlusion developed anterior segment neovascularization. This proved more sensitive than initial fluorescein angiography, probably because some of these eyes converted later to nonperfusion.

PEARL... The presenting visual acuity is the most reliable predictor for NVG following CRVO.

TABLE 21-1 MECHANISMS OF ANTERIOR SEGMENT NEOVASCULARIZATION AND PREDISPOSING CONDITIONS

Retinal Ischemia	Retinal Detachment	Ocular Inflammation	Intraocular Tumors
Central retinal vein occlusion	Chronic traction retinal detachment	Chronic uveitis	Choroidal melanoma
Diabetic retinopathy	Proliferative vitreoretinopathy	Retinal vasculitis	Iris melanoma
Extraocular vascular disease (carotid artery occlusion)	Coats' exudative retinopathy	Trauma	Retinoblastoma
Sickle cell retinopathy	Retinoschisis	Anterior segment ischemia	Metastatic disease (rare)
Central retinal artery		Endophthalmitis	
Radiation treatment			
Retinopathy of prematurity			
Eales disease			
Familial exudative vitreoretinopathy			
Persistent hyperplastic primary vitreous			

TABLE 21-2 RISK OF ANTERIOR SEGMENT NEOVASCULARIZATION AND RETINAL NONPERFUSION BY PRESENTING VISUAL ACUITY (CENTRAL VEIN OCCLUSION STUDY)

<i>Presenting Visual Acuity</i>	<i>Neovascularization (%)</i>	<i>Nonperfusion* (%)</i>
20/40 or better	5	4
20/50–20/200	15	17
Less than 20/200	31	61

* Greater than 10 disc areas of capillary nonperfusion on fluorescein angiography.

Other tests also associated with the development of NVG include measuring digital venous pressure, the electroretinogram,¹⁴ and the afferent pupillary defect.¹⁵ However, in the CVOS, none of these provided additional prognostic information beyond that obtained from routine clinical examination, and especially the presenting visual acuity.⁹

The occurrence of CRVO in one eye carries a significant risk for the other eye. In the CVOS, nearly 10% of patients already had an occlusion in the fellow eye at the time of enrollment.⁹ Among the remaining patients, approximately 1% per year suffered a subsequent occlusion in the second eye. Bilateral CRVO, while rare, suggests the possibility of a systemic disorder.

Preeexisting glaucoma may significantly contribute to CRVO. Approximately 25% of all patients with CRVO have concomitant open-angle glaucoma, with an even higher incidence in elderly patients.^{12,16} In these patients, CRVO may result directly from the effect of elevated IOP on blood vessels. Alternatively, compression and connective tissue remodeling of the glaucomatous lamina cribrosa could produce mechanical distortion of the central retinal vein, particularly if associated with arterial sclerosis. This is supported by pathologic observations of a central retinal vein thrombus in a high proportion of eyes with CRVO.¹⁷

Hemiretinal vein occlusion can also cause NVG.^{18,19} However, this is relatively unlikely given that the risk of anterior segment neovascularization is proportional to the extent of nonperfusion.

Diabetic Retinopathy

The association of iris neovascularization with diabetes mellitus generally increases with the duration of the disease, and particularly with the development of proliferative diabetic retinopathy.^{20,21} Iris neovascularization is common in diabetes, and, although pupillary vascular tufts can appear, they do not necessarily progress to NVG.

NVG may develop in diabetics following cataract surgery, either with or without lens implantation. The risk is greatest with intracapsular surgery, particularly in the face of active retinopathy.²² However, extracapsular and phacoemulsification techniques can also result in NVG, although this is much less likely if the posterior capsule remains intact.^{23–25} Because NVG can also follow yttrium-

aluminum-garnet (YAG) capsulotomy in diabetics,²⁶ glaucoma after cataract surgery probably results from a combination of surgical inflammation and disruption of a barrier preventing diffusion of angiogenesis factors to the anterior segment, as discussed in the following text. Although active proliferative retinopathy at the time of cataract surgery clearly encourages NVG, and preoperative panretinal photocoagulation (PRP) can ameliorate this,²⁷ the glaucoma risk increases even if retinopathy is quiescent.^{28,29}

NVG can also develop following vitrectomy and lensectomy for diabetic retinopathy.^{30–32} This increased risk may result from both improved anterior diffusion of angiogenesis factors and chronic retinal detachment,³³ which can follow diabetic vitrectomy and may itself contribute to retinal hypoxia.

Extraocular Vascular Disease

Vascular diseases extrinsic to the eye, particularly carotid artery occlusion, can also produce retinal hypoxia. Although it can contribute to CRVO and proliferative diabetic retinopathy, carotid artery occlusion, by itself, represents the third most common of all causes of NVG.^{34,35} Because this artery supplies both the anterior and the posterior ocular circulation, the resulting ischemia can impair ciliary body perfusion and decrease aqueous humor formation. This produces a paradoxically low IOP in eyes with NVG^{36,37} and can diminish retinopathy on the side of the occlusion in diabetics with proliferative retinopathy. Although carotid stenosis is the most common extraocular vascular disease associated with NVG, other causes include carotid-cavernous sinus fistula,³⁸ embolic therapy of dural-cavernous sinus shunts,³⁹ and temporal arteritis.⁴⁰

Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) probably causes NVG by decreasing retinal perfusion. However, occlusion of the central retinal artery alone should destroy the inner retina and diminish production of angiogenic factors. Thus, NVG from CRAO probably requires additional risk factors, such as carotid occlusive disease,⁴¹ which can also predispose to CRAO. Because this condition can also coexist with CRVO, the true incidence of glaucoma from CRAO alone is uncertain, but is estimated between 5 and 10%.⁴²

Retinal Detachment

Retinal detachment may produce neovascularization by releasing angiogenic factors from the detached retina or retinal pigment epithelium. However, associated ischemia and chronic inflammation may also contribute.⁴³ Following vitrectomy, chronic traction detachment is the main cause of NVG in both diabetic and nondiabetic patients.³³ Paradoxically, successful retinal detachment surgery may cause neovascularization⁴³ due to anterior segment ischemia from trauma to the anterior ciliary arteries and direct effects of the scleral buckle on the choroidal circulation.

Uveitis

Ocular inflammation likely produces neovascularization via the release of angiogenic factors.³⁴ Posterior uveitis and scleritis are more likely to produce NVG than iridocyclitis, due to their increased severity and greater propensity to affect retinal vascular perfusion.⁴⁴

Tumors

Malignant melanoma and retinoblastoma are the most common tumors associated with iris neovascularization and NVG.^{45,46} With the former, this association is related to larger tumor size, secondary retinal detachment, and necrosis,⁴⁷ whereas the latter promotes NVG by compromising large retinal vessels and infiltrating the retina.⁴⁸ Hypoxia and production of angiogenic factors probably account for this glaucoma in both types of tumors.

MECHANISMS OF NEOVASCULARIZATION

The association of NVG with poor retinal perfusion suggests that new blood vessels form in response to a diffusible growth factor produced by the oxygen-starved retina.⁴⁹ The early appearance of neovascularization at the pupillary border and its regression following ablation of the peripheral retina support this concept. Similar growth factors may also explain anterior segment neovascularization in eyes with intraocular tumors and uveitis.⁵⁰

Many identified growth factors probably act in concert to produce new blood vessels. This involves increased permeability of vascular endothelial cells, focal dissolution

of the surrounding extracellular matrix, and eventual division and migration of the endothelium to form neovascular branches that spread through the iris and anterior chamber angle.

Vascular endothelial growth factor (VEGF) is currently the most prominent of these factors and has been found to promote several stages of the neovascular cascade. Increased levels of VEGF occur with iris neovascularization in both diabetics and patients with CRVO⁵¹ and in monkey eyes with experimental CRVO.⁵² Other growth factors that may promote neovascularization include acidic and basic fibroblastic growth factor,⁵³ and transforming growth factor-alpha and beta. Prostaglandins may also participate, possibly by mediating other angiogenesis factors.⁵⁴ Better understanding of these factors, and others, will eventually lead to specific therapies that reduce their activity and prevent neovascularization.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The signs and symptoms of neovascularization vary with the stage of the disease (Table 21–3). Early symptoms usually consist of decreased visual acuity from the underlying retinal condition, and, occasionally, from corneal epithelial edema and anterior chamber inflammation if retinal function is normal. Later symptoms include ocular discomfort, brow ache, and nausea from inflammation and elevated IOP.

The anterior segment signs of neovascularization and NVG appear in Figure 21–2A–E. Iris neovascularization usually begins at the pupillary border and then spreads as matted, irregular vessels over the anterior surface of the iris, which may appear unusually smooth, due to the associated, clinically invisible fibrous membrane (Fig. 21–1).⁶

Angle neovascularization either follows or accompanies (but occasionally precedes) iris involvement, initially as fine vessels in the ciliary body band, with branches crossing the scleral spur and arborizing within the trabecular meshwork. Peripheral anterior synechiae form, due to membrane contraction, and then coalesce to “zipper” up the anterior chamber angle. Further contracture of the membrane on the anterior iris drags the iris pigment epithelium through the pupil, causing ectropion uveae.

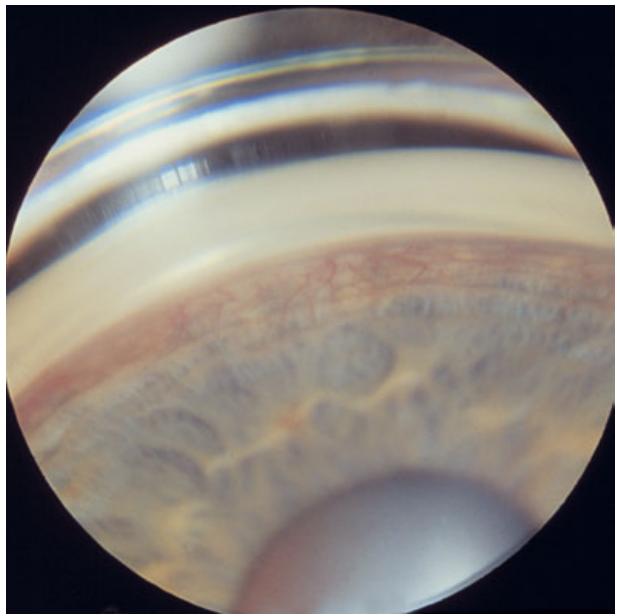
TABLE 21–3 DIAGNOSIS OF NEOVASCULAR GLAUCOMA

	<i>Early</i>	<i>Late</i>
Symptoms	Decreased acuity	Brow ache Nausea
Signs	Pupillary neovascularization Iris neovascularization Angle and trabecular meshwork neovascularization	Angle closure Ectropion uvea Anterior chamber inflammation Elevated IOP

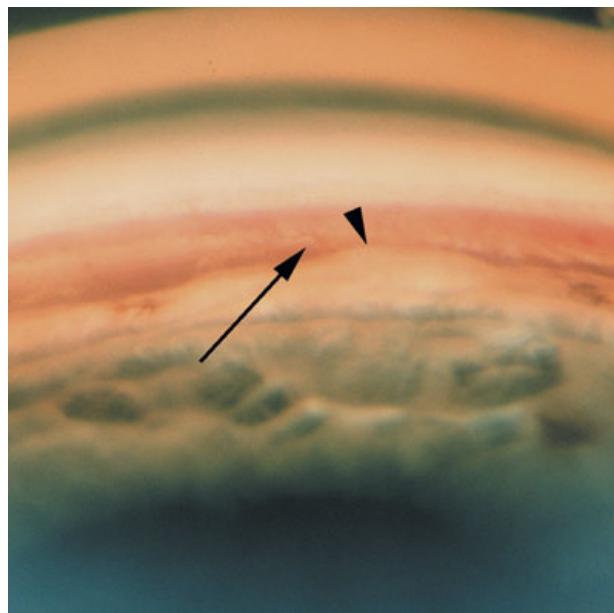
IOP, intraocular pressure.



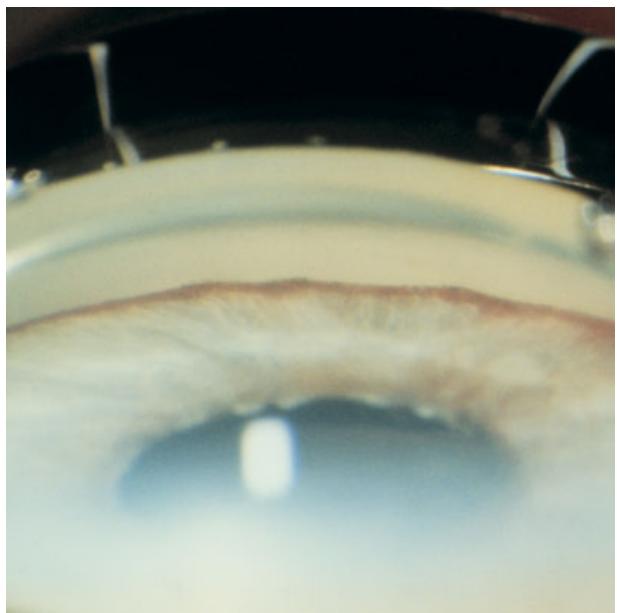
A



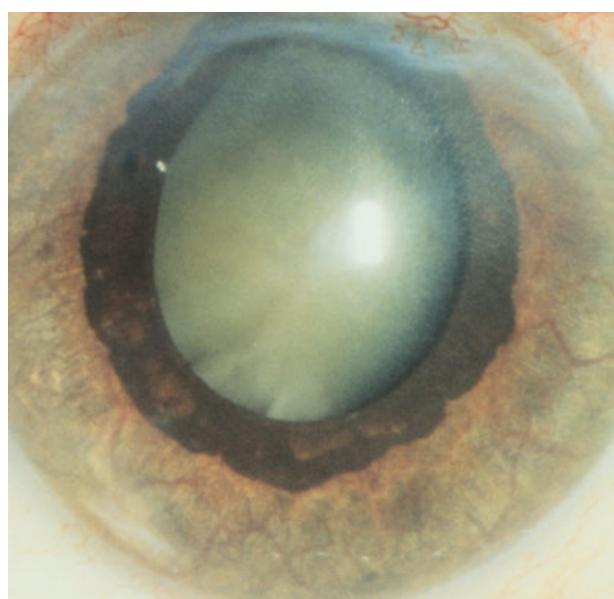
B



C



D



E

FIGURE 2I-2 Anterior segment neovascularization usually begins with (A) peripupillary vessels and (B) extends over the iris surface. (C) Chamber angle vessels (arrow) cross the scleral spur and arborize in the trabecular meshwork, with later contraction of the fibrovascular membrane to produce peripheral synechiae (arrowhead). (D) Further membrane contraction causes total angle closure and (E) in advanced cases, ectropion uvea by pulling the iris pigment epithelium anteriorly through the pupil.

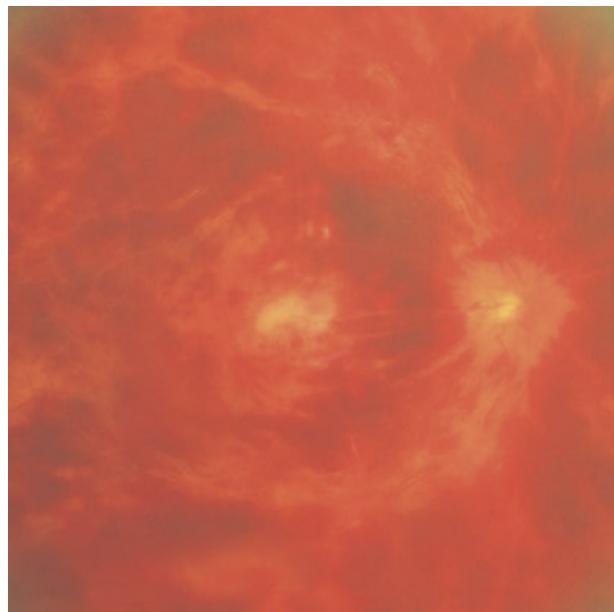
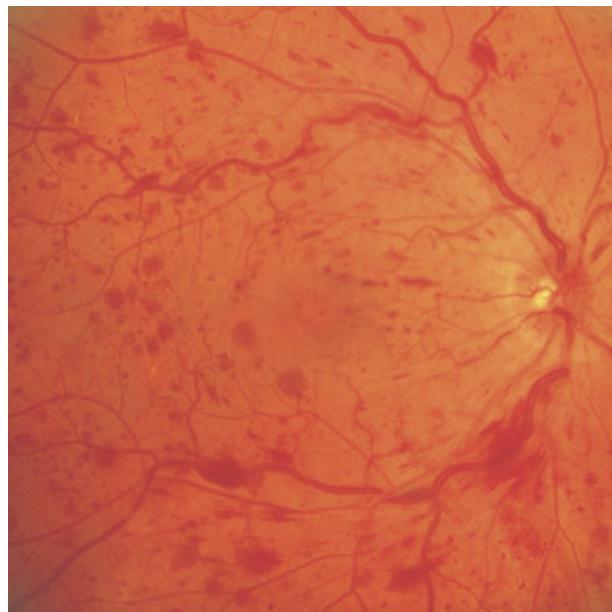


FIGURE 21-3 The spectrum of retinal findings from central retinal vein occlusion (CRVO) appear in a patient (A) with an initially perfused CRVO, that converted later to (B) nonperfusion.

Although glaucoma typically results from angle closure, the fibrovascular membrane alone can also obstruct aqueous humor outflow, causing elevated IOP with a clinically open angle. Alternatively, IOP may be normal despite extensive neovascularization and angle closure if due to carotid occlusive disease and ocular ischemia, as already mentioned.^{36,37} Corroborative findings include retinal arterial pulsations, asymmetric diabetic retinopathy, and persistence of neovascularization despite extensive PRP.

SPECIAL CONSIDERATION

Normal intraocular pressure with rubeosis and angle closure, poor response to panretinal photocoagulation, or markedly asymmetric diabetic retinopathy may all indicate extraocular vascular obstruction, most likely from carotid artery disease.

The optic nerve can appear normal, if elevated IOP is relatively recent, although disc edema, hemorrhage, or neovascularization may result from the underlying ocular condition. Extensive glaucomatous cupping indicates pre-existing, advanced glaucoma, along with ciliary shunt vessels (Chapter 10, Fig. 10-11), which may also follow retinal vascular occlusions. The occurrence of a CRVO in one eye always raises the possibility of open-angle glaucoma and should prompt careful evaluation of the fellow eye for glaucoma and vigorous treatment if found.⁵⁵

Retinal findings often indicate the underlying cause of the neovascularization, such as vascular congestion

and intraretinal hemorrhages if due to CRVO (Fig. 21-3A,B), or proliferative diabetic retinopathy. Vitreous hemorrhage may obscure the retinal pathology in any of these conditions.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of NVG includes uveitis, acute and chronic angle closure, and other conditions that may produce neovascularization and cause glaucoma in their own right (Table 21-4).

Severe anterior uveitis can produce dilated iris vessels and elevated IOP. Unlike neovascularization, these vessels typically are radially arranged, suggesting that they are engorged, but otherwise part of the normal, iris

TABLE 21-4 DIFFERENTIAL DIAGNOSIS OF NEOVASCULAR GLAUCOMA

Condition	Differentiating Features
Uveitis*	Radial, engorged iris vessels, cells, flare Keratic precipitates
Acute angle closure	Pupillary block iris contour, hyperopia Lack of neovascularization Lack of retinal pathology
Chronic angle closure	Lack of neovascularization Lack of retinal pathology
Retinal detachment*	Fundus pathology
Intraocular tumors*	Fundus pathology
Postretinal detachment repair*	History of scleral buckle surgery Angle closure

*May, itself, cause neovascular glaucoma.

vasculature. Because uveitis can also induce true neovascularization, detection of an open angle favors uveitis as the cause of glaucoma. Fine angle vessels may also occur in Fuchs' heterochromic iridocyclitis, but without generalized iris involvement and angle closure.

Although acute angle closure can cause rapid IOP elevation, the pupillary block contour of the iris, lack of neovascularization, and lack of obvious retinal pathology distinguish this condition from NVG. A hyperopic refractive error and gonioscopy of the fellow eye usually leads to the correct diagnosis.

Iris neovascularization may be less apparent in eyes with elevated IOP, or advanced NVG, due to decreased corneal clarity and diminished perfusion of the fine new vessels from the elevated IOP. These cases must be differentiated from other causes of chronic angle closure and iris distortion, such as trauma or the iridocorneal endothelial (ICE) syndromes.

NVG must also be differentiated from causes of NVG that can produce glaucoma on their own, particularly when neovascularization, peripheral anterior synechiae, and retinal nonperfusion are less prominent than might otherwise be expected in NVG. In addition to uveitis, these include intraocular tumors, retinal detachment, and glaucoma following retinal detachment repair. Identifying these conditions usually follows a diligent search for the underlying causes of neovascularization. This includes careful ophthalmoscopy in eyes without evidence of diabetic retinopathy or CRVO, and ultrasound if the view of the posterior pole is poor.

MANAGEMENT

Preventing neovascularization is the most successful treatment for NVG. This depends on early detection of the predisposing conditions, surveillance for iris neovascularization, and early, aggressive management if found. Advances in PRP have also improved the outcome of incisional surgery for NVG, particularly if combined with antimetabolites.

SURVEILLANCE

The CVOS provides several recommendations for early detection of anterior segment neovascularization following CRVO.⁹ These include careful slit-lamp examination and gonioscopy prior to dilation at the initial visit, along with tonometry. Presence of iris or angle neovascularization, with or without elevated IOP, should prompt immediate, aggressive PRP.

PEARL... Presence of iris or angle neovascularization following central retinal vein occlusion should prompt immediate, aggressive panretinal photocoagulation, regardless of eye pressure.

If there is no evidence of rubeosis, and IOP is normal, visual acuity is the best predictor of ultimate neovascularization.⁹ Occasionally, fluorescein angiography may help if the clinical findings are inconsistent, such as an elevated IOP without apparent neovascularization. However, angiography is usually not helpful because patients who are initially perfused can still develop NVG (Fig. 21-3A,B), and require close observation.

If acuity is 20/40 or better, examine the patient every 1 to 2 months for the first 6 months, and then taper the frequency to annual examinations (Table 21-5). If acuity is 20/200 or less, examine the patient monthly for the first 6 months, tapering to annual examinations. If acuity is between 20/50 and 20/200, exams should be performed either monthly or bimonthly, depending on where the acuity falls in this range. Patients should report any acuity change immediately, at which time they should be examined and monthly checkups begun if visual acuity falls to 20/200 or less. Each follow-up examination should include tonometry, a biomicroscopic evaluation of the pupillary border without dilation, and gonioscopy given that angle neovascularization can occur even without iris involvement.⁵⁶

PITFALL... Omitting gonioscopy may delay timely panretinal photocoagulation because 10% of eyes with angle neovascularization following central retinal vein occlusion lack iris rubeosis.

In diabetes, NVG is nearly always associated with proliferative retinopathy, which parallels the duration of the disease and blood sugar control. Thus, optimal detection of NVG in diabetes relies on annual dilated fundus examinations, which are already recommended for detecting proliferative diabetic retinopathy. Small capillary tufts at the pupillary border, suggestive of early rubeosis, may occur in diabetes. In the absence of proliferative retinopathy, however, these should simply be observed for progression. Patients requiring cataract

TABLE 21-5 SURVEILLANCE FOR ANTERIOR SEGMENT NEOVASCULARIZATION FOLLOWING CENTRAL RETINAL VEIN OCCLUSION*

Presenting Visual Acuity	Examination Interval
20/40 or better	Every 1 to 2 months for first 6 months Taper to annual
20/50 to 20/200	Every 1 to 2 months for first 6 months Taper to annual
20/200 or less	Monthly for first 6 months Taper to annual

* Examinations include tonometry, slit-lamp biomicroscopy, and gonioscopy.

extraction should be evaluated for proliferative retinopathy and receive adequate PRP prior to surgery, if possible.

NVG following central retinal artery occlusions may occur within weeks of the occlusion. Monthly examinations for anterior segment neovascularization are recommended for the first 6 months following this event.

In carotid occlusive disease, PRP may not significantly affect anterior segment neovascularization and NVG because of generally reduced ocular perfusion. Although carotid endarterectomy can decrease the risk of NVG,⁵⁷ the improved ocular perfusion can also enhance aqueous humor formation and exacerbate glaucoma.^{36,58} In general, the morbidity of endarterectomy limits its use to patients with neurologic symptoms, in whom it may significantly reduce the risk of stroke or death.

PANRETINAL PHOTOCOAGULATION

As with proliferative diabetic retinopathy, using PRP to eliminate production of the vasoproliferative stimulus by the peripheral retina can diminish or eliminate anterior segment neovascularization due to CRVO and proliferative diabetic retinopathy.^{59,60} The effect is less significant on neovascularization following CRAO and carotid disease.^{61,62}

The exact mechanism of action for PRP is unknown. It is possible that the laser simply decreases the total amount of retina available to produce angiogenic factors. Decreased production of these factors may also result from retinal thinning (through damage to photoreceptors and retinal pigment epithelium) and improved oxygen delivery to the inner retina.⁴²

PEARL... Because eyes with nonperfusion or poor visual acuity do not always develop anterior segment neovascularization, high-risk eyes should be monitored for this complication before performing panretinal photocoagulation.

Treatment usually includes at least 1,500 laser spots outside the vascular arcades, although many patients require more extensive treatment (Fig. 21-4). Sessions can be divided, either with or without retrobulbar anesthesia because extensive treatment (generally over 1,000 spots for a single session) may induce suprachoroidal effusion, anterior rotation of the ciliary body, and acute angle closure (Chapter 27). Following laser, topical steroids can be used along with continued glaucoma therapy. Close follow-up is essential, usually within 10 days, to monitor the response to laser and detect early progression to NVG. If regression fails to occur, or if neovascularization progresses further, timely PRP is usually effective.

Alternative laser methods include indirect PRP, usually with retrobulbar anesthesia, which can allow more peripheral retinal treatment, and either argon or diode endolaser if a vitrectomy is already planned. If corneal

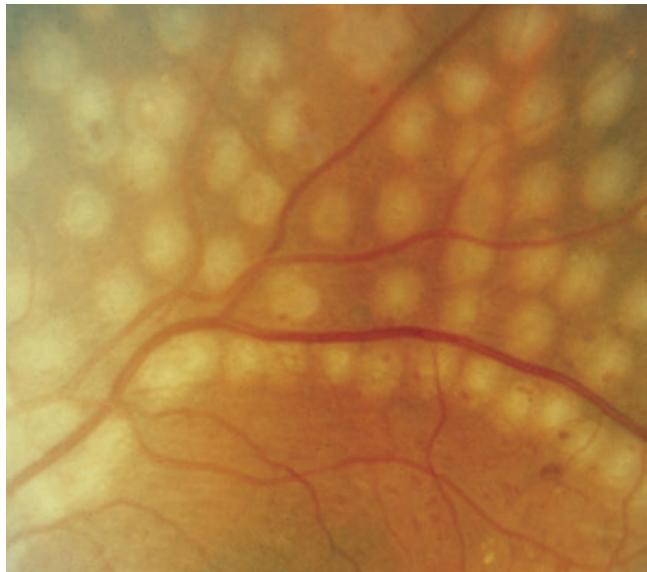


FIGURE 21-4 Fundus immediately following panretinal photocoagulation shows appropriate intensity and spacing of laser spots. (Courtesy of Early Treatment Diabetic Retinopathy Study.)

epithelial edema, cataract, or inflammation obscure the fundus, peripheral retinal cryotherapy can effectively treat neovascularization,⁶³ although it may increase inflammation and cause retinal detachment.

Another approach, goniophotocoagulation, obliterates new vessels in the angle as they cross the scleral spur.⁶⁴ However, without PRP this procedure does not prevent synechial angle closure, and it is rarely indicated.

MEDICAL MANAGEMENT OF NEOVASCULAR GLAUCOMA

Management of established NVG requires aggressive pressure treatment when beginning PRP. This includes topical and oral glaucoma therapy as well as hyperosmotic agents as allowed by the patient's medical condition. Because elevated IOP can result from meshwork obstruction by the fibrovascular membrane alone, PRP prior to angle closure can occasionally control pressure and reduce or eliminate the need for chronic glaucoma treatment.

SPECIAL CONSIDERATION

Aggressive panretinal photocoagulation prior to total angle closure may control glaucoma and prevent the need for filtering surgery, even in the presence of extensive neovascularization of the trabecular meshwork.

Chronic medical treatment for NVG includes topical beta-blockers and alpha agonists and either topical or oral carbonic anhydrase inhibitors (Table 21-6). Cholinergic agents may be less effective if the anterior chamber angle

TABLE 21-6 MEDICAL MANAGEMENT OF NEOVASCULAR GLAUCOMA

Topical aqueous humor suppressants
Oral carbonic anhydrase inhibitors (if medical condition allows)
Osmotic agents for acute IOP control and systemic symptoms
Topical steroids
Topical cycloplegics
Cholinergic agents and prostaglandin analogs doubtful

is already closed. The use of prostaglandin analogs in NVG is not yet established, although they may have similar limitations and may exacerbate ocular inflammation.

Adjunctive treatment includes topical steroids to help control inflammation, slow proliferation of the fibrovascular membrane, and improve the outcome of subsequent filtration surgery. Cycloplegics improve patient comfort and increase visibility of the fundus for PRP.

SURGICAL MANAGEMENT OF NVG

Until recently, surgery was limited to cyclocryotherapy. The advent of PRP and recent advances in filtration surgery with antimetabolites and valve implantation have markedly improved the prognosis of NVG.

Following adequate PRP, standard trabeculectomy with adjunctive antimetabolites can successfully control IOP.^{65,66} Allowing time for resolution of the neovascularization before surgery enhances the long-term success of filtering surgery. However, in urgent situations, indirect PRP with retrobulbar anesthesia immediately prior to trabeculectomy or valve implantation can also be effective.

Filtration surgery for NVG is similar to that described for trabeculectomy with antimetabolites. Sudden decompression of the globe after paracentesis may result in anterior chamber hemorrhage during and after surgery, which may encourage filter failure and complicate any subsequent PRP. Direct cautery of iris vessels prior to iridectomy may decrease the chance of intraocular hemorrhage.

Valves, or setons, can also lower IOP in NVG, particularly if preceded by PRP.⁶⁷ Although not as low as that achieved with filtration, pressure control with these devices is often sufficient because many of these eyes do not have extensive optic nerve damage.

CONTROVERSY

Many surgeons choose cyclophotocoagulation for neovascular glaucoma because these patients have poor visual prognosis. However, both valve implantation and filtration surgery may be preferred in selected individuals because they provide more rapid control of IOP and pain relief.

Although trabeculectomy and valve implantation can control NVG, both require a full surgical setting and carry

the risks of intraocular surgery. Because poor visual prognosis may not justify these risks, many authorities recommend ciliary body destruction for patients with NVG. Both YAG and diode laser techniques are effective and are discussed in Chapter 42.⁶⁸ Complications, primarily hypotony, are much lower with both approaches than with cyclocryotherapy.⁶⁹ However, eyes with total angle closure and minimal aqueous humor outflow often require repeated treatments, although postoperative inflammation can be painful. In certain patients, filtration surgery and valve implantation offer more definitive IOP control and immediate pain relief.

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IRIDOCORNEAL ENDOTHELIAL SYNDROME

Annapurna Singh, M.D., and Jody R. Piltz-Seymour, M.D.

The iridocorneal endothelial (ICE) syndrome represents a broad spectrum of ocular diseases with the common denominator of an abnormal corneal endothelium and a collagenous membrane posterior to Descemet's. They are characterized by varying degrees of corneal edema, progressive alterations in the iris, angle abnormalities, and they are often associated with glaucoma. The major clinical variations are the Chandler's syndrome, progressive (essential) iris atrophy, and the Cogan-Reese syndrome. These are differentiated from each other by the relative prominence of corneal and iris findings.

Glaucoma occurs in half of all patients with ICE syndrome, probably due to gradual extension of the membrane over the angle structures. It is more severe in patients with progressive iris atrophy and Cogan-Reese syndrome than in Chandler's syndrome.¹ Patients with ICE syndrome require treatment for glaucoma, corneal edema, or both. Although medical glaucoma treatment may be effective in early cases, most patients eventually require surgery and, often, a repeat procedure.¹

BACKGROUND

In 1903, Harms and Aulhorn first described a form of glaucoma associated with iris hole formation and atrophy of the iris.² Chandler reported similar, but less severe, cases in 1956, with the additional finding of corneal edema, even with normal or slightly elevated intraocular pressures.³ He also described an abnormal, "hammered silver" appearance to the corneal endothelium, and this condition came to be known as Chandler's syndrome. In 1969, Cogan and Reese reported two patients with pigmented iris nodules that underwent enucleation for suspected iris melanomas.⁴ Similar lesions were later found in essential iris atrophy and Chandler's syndrome. In 1975, Scheie and Yanoff described a similar condition

with iris nevi, that they called iris nevus syndrome.⁵ However, these iris lesions are histologically distinct from the Cogan-Reese syndrome.

In 1979, Eagle et al. observed that the common denominator in essential iris atrophy, Chandler's syndrome, and Cogan-Reese syndrome was a corneal endothelial abnormality that extended to involve the iris.⁶ They proposed the term *iridocorneal endothelial (ICE) syndrome*, and this is currently the most accepted term for this group of diseases. Chandler's syndrome is the most common variant of ICE syndrome. It accounts for about 50% of all of these patients, whereas progressive iris atrophy and Cogan-Reese syndrome account for approximately 25% each.⁷

PEARL... Essential iris atrophy, Chandler's syndrome, and Cogan-Reese syndrome are related by the common denominator of a corneal endothelial abnormality that extends over the iris surface.

The ICE syndrome is a group of sporadic disorders with rare cases of familial involvement.⁸ There is no known association with a systemic disease, and they are generally considered to be acquired conditions.

PATHOGENESIS

PATHOLOGY

Abnormalities are found in the cornea, anterior chamber angle, and iris. Light microscopic studies reveal a collagenous layer consisting of a normal-appearing Descemet's membrane bound posteriorly by thickened layers of banded and fibrillar collagen tissue and a lining of abnormal cells.⁹ The endothelium may be present in some areas

and replaced in others by these abnormal cells. Immunocytochemical evidence of epithelial features within the membranous tissue is conflicting.^{9–11} Ultrastructurally, these cells line a multilayered collagenous tissue posterior to Descemet's membrane.^{12,13} In some areas, the cells are multilayered, suggesting loss of contact inhibition, although a single layer is more typical. In other areas, cells are absent altogether, exposing the underlying collagen. In some studies, these cells are well differentiated, with epithelial features such as desmosomes, tonofilaments, and microvilli.¹⁴ Other studies suggest that ICE cells are similar to normal limbal epithelial cells, and they may develop from an embryologic ectopia of ocular surface epithelium. An alternate hypothesis is that a metaplastic stimulus alters the phenotype of normal corneal endothelial cells.^{10,15}

In the angle, a cellular membrane has been described that extends from the peripheral cornea to cover some areas of open angle and others closed by peripheral anterior synechiae. This membrane appears to consist of a single layer of endothelial cells and a Descemets-like membrane. The extent of disease on the posterior surface of the cornea and that on the iris do not appear to be correlated.

Histopathology of the iris includes a cellular membrane on the anterior surface of the iris, which is often continuous with the membrane covering the angle structures.¹⁶ Atrophy of the iris and hole formation is observed in progressive iris atrophy. Although blood vessel basement membranes are thickened, there is no evidence of vascular occlusion.^{17,18} In Chandler's syndrome, the histopathology is the same, although the iris atrophy is minimal and hole formation is rare. In Cogan-Reese syndrome, the cellular membrane surrounds the pedunculated iris nodules, which have a structure similar to the iris stroma.

PATHOGENESIS OF GLAUCOMA

The exact etiology of glaucoma is unknown. However, all the features associated with the ICE syndrome can be attributed to an abnormal membrane on the posterior cornea that grows over the angle structures and the iris. Contraction of the membrane, with or without formation of peripheral anterior synechiae, is probably responsible for the secondary glaucoma.¹⁹ The iris nodules in Cogan-Reese syndrome may occur when this membrane pinches off parts of the iris stroma.

The presence of a chronic, low-grade corneal inflammation with lymphocytes suggests the possibility of a viral etiology for the ICE syndrome. This may explain the lack of familial and congenital cases and also the fact that the corneal alterations appear in the postnatal period. One study implicated the Epstein-Barr virus while another study suggested a role for herpes simplex.^{20,21} However, neither study firmly established a causative role for these agents. On polymerase chain reaction (PCR) testing, her-

pes simplex viral DNA has been identified in the corneal endothelium, iris, and trabecular meshwork in patients with ICE syndrome. Should this theory prove correct, antiviral drugs could be used to treat the corneal endothelial cell infection in early cases to prevent the development of the endothelial membrane.²¹

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The ICE syndrome is generally unilateral, although some bilateral cases have been reported.^{16,18} It is more commonly seen in middle-aged women. The presenting feature is either pain or blurred vision, which is often intermittent and is related to the corneal edema. Initially, this may be worse in the mornings and improve over the course of the day. In the later stages of the disease, vision may not improve due to persistent corneal edema or due to glaucomatous optic atrophy. Some patients present after noticing a distorted shape of the iris or development of a "second pupil."

Clinical examination reveals a beaten metal appearance of the corneal endothelium (Fig. 22–1A). On slit-lamp specular reflection, there is prominence of the intercellular spaces, which makes the cell borders appear darker and wider. Specular photomicroscopy reveals a diffuse abnormality of the corneal endothelium with "ICE" cells. These cells have varying degrees of pleomorphism and loss of hexagonal margins and characteristically contain dark areas.²² Four patterns of clinical appearance have been described²³: (1) total ICE, in which ICE tissue covers the posterior cornea completely and no normal endothelial cells are apparent; (2) disseminated ICE, where ICE cells are scattered throughout poorly defined enlarged endothelial cells; (3) subtotal ICE plus, where an area of ICE tissue is well demarcated from abnormally small endothelial cells; and (4) subtotal ICE minus, in which ICE tissue merges with abnormally large endothelial cells. In most case reports, isolated areas of abnormal cells progress to eventually cover the entire posterior cornea. In one report, however, these cells regressed completely.²⁴ The contralateral eye also often exhibits islands of endothelial abnormality.²⁵ Confocal microscopy, which can reveal epithelial-like endothelial cells with hyperreflective nuclei, may be useful in cases with corneal edema.²⁶

The iris has varying degrees of atrophy and hole formation. Peripheral anterior synechiae are typically broad, attach anteriorly on the cornea, and usually obliterate the angle structures (Fig. 22–1B,C). Glaucomatous nerve and field changes may be apparent at the initial presentation. Glaucoma is often but not always related to the amount of peripheral anterior synechiae.

In Chandler's syndrome, the corneal changes usually predominate, with minimal to mild iris changes (Table 22–1). In progressive iris atrophy, the iris changes are predominant. They may begin with mild corectopia but



FIGURE 22-1 Chandler's syndrome. (A) Specular reflection reveals characteristic "beaten metal" appearance of corneal endothelium. (B) Moderate corneal edema, iris distortion, and anterior synechiae. (C) Gonioscopy in another patient demonstrates peripheral synechiae. [(B) Courtesy of E. Michael Van Buskirk, M.D.]

TABLE 22-1 CLINICAL SPECTRUM OF IRIDOCORNEAL ENDOTHELIAL SYNDROME

Feature	Cornea	Iris	Glucoma
Chandler's syndrome	Edema	Minimal changes	Mild
Essential iris atrophy	Clear	Atrophic holes	Severe
Cogan-Reese syndrome	Clear/edema	Iris nodules	Severe

progress to stretch holes and melting holes of the iris stroma (Fig. 22-2A,B). Stretch holes occur in the quadrant opposite the iris contraction and the corectopia. Melting holes are not associated with iris distortion and may be due to iris ischemia. In Cogan-Reese syndrome, the characteristic pigmented, pedunculated iris nodules are seen with varying degrees of corneal and iris involvement (Fig. 22-3A,B). The intervening iris surface typically appears flat, due to the membrane on its anterior surface.

Glaucoma occurs in 46 to 89% of patients with ICE syndrome and is more common when abnormal cells cover the entire posterior cornea.^{1,27-29} It is worse in patients with progressive iris atrophy and Cogan-Reese syndrome.

DIFFERENTIAL DIAGNOSIS

Various conditions associated with iris and corneal abnormalities, and secondary glaucoma may mimic ICE syndromes (Table 22-2). The clinician should always suspect ICE syndrome in a young patient with unilateral glaucoma.

PEARL... The clinician should always suspect iridocorneal endothelial syndrome in a young person with unilateral glaucoma and no history of trauma or uveitis.

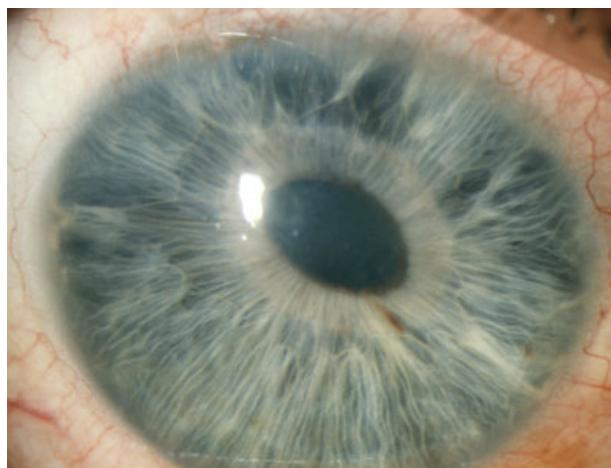
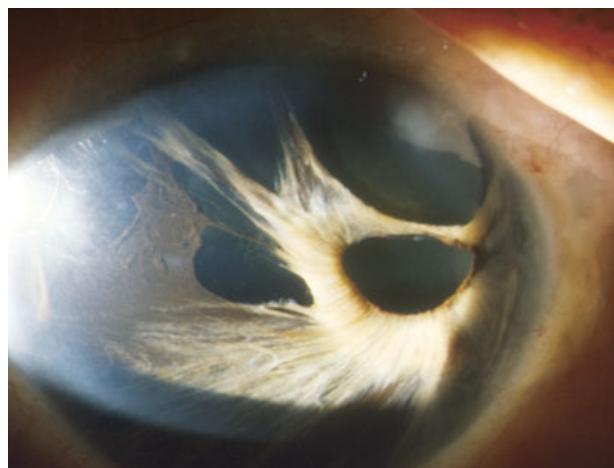
**A****B**

FIGURE 22-2 Essential iris atrophy. (A) This patient presented with epithelial edema and only mild iris and pupil distortion, and was initially diagnosed as Chandler's syndrome. (B) Same eye, 6 years later, demonstrates marked corectopia, with iris stretching, atrophy, and hole formation in the opposite quadrant.

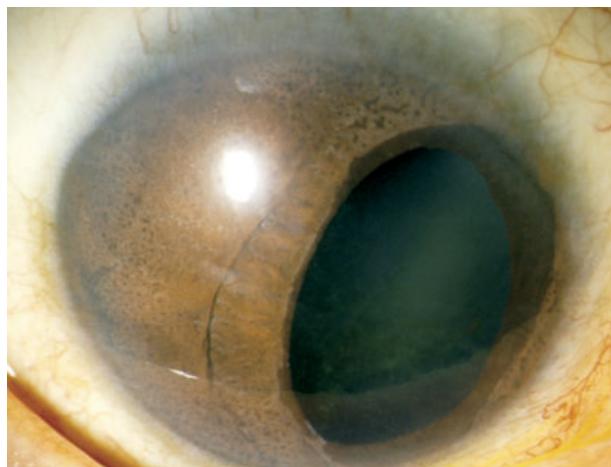
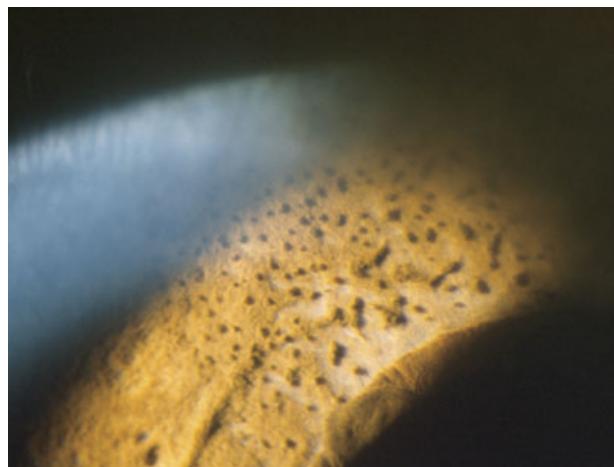
**A****B**

FIGURE 22-3 Cogan-Reese syndrome. (A) This eye initially presented with only mild corectopia, but over the next 3 years developed epithelial edema; marked pupillary distortion; and diffuse, fine iris nodules. (B) High power photograph demonstrates pedunculated iris nodules with a flattened iris surface in between.

TABLE 22-2 DIFFERENTIAL DIAGNOSIS OF IRIDOCORNEAL ENDOTHELIAL SYNDROME

Corneal Disease	Iris Diseases
Posterior polymorphous dystrophy	Axenfeld-Rieger syndrome
Fuchs' corneal dystrophy	Aniridia
	Iridoschisis
	Lisch nodules
	Iris mammillations
	Diffuse iris melanoma

Corneal disorders that mimic ICE syndrome are Fuchs' corneal dystrophy and posterior polymorphous dystrophy (PPD). Both of these conditions are bilateral and often are familial, but differ in their specular microscopic appearance. In ICE syndrome, small dark areas appear within the cell

margins, whereas in PPD there are large, irregular dark areas that cross over from one cell to the next. PPD is also generally nonprogressive. It is recognized by characteristic vacuoles at the level of Descemet's membrane (Fig. 22-4). Although uncommon, glaucoma can occur due to growth of an abnormal endothelial membrane across the anterior chamber angle, occasionally with iris and pupil distortion. Fuchs' syndrome does not have any angle or iris abnormalities.

Iris disorders that mimic ICE syndrome include the Axenfeld-Rieger syndrome. This condition is generally bilateral and congenital and is often associated with skeletal and dental abnormalities. Aniridia and iridoschisis may also occasionally mimic the ICE syndromes. Lisch nodules, iris mammillations, and diffuse iris melanoma may be mistaken for the nodular lesions of Cogan-Reese syndrome. At present, most authorities do not consider the iris nevus syndrome part of the ICE syndrome.

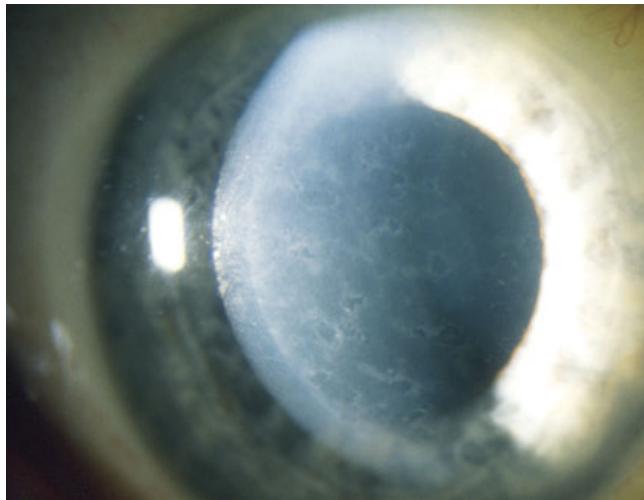


FIGURE 22-4 Posterior polymorphous dystrophy, which can occasionally be associated with glaucoma, is in the differential diagnosis of iridocorneal endothelial syndrome.

MANAGEMENT

GLAUCOMA

In the early stages of the disease, the glaucoma may be controlled medically, particularly with aqueous humor suppressants. Medications that work on the trabecular outflow mechanism are not effective. In the later stages, medical therapy usually fails in controlling the intraocular pressure, and surgery is indicated. Argon laser trabeculoplasty should be avoided because it is not effective and may potentially stimulate proliferation of the retrocorneal and iris membrane.

Most authors agree that eventually surgical treatment will be necessary. In one study, filtering surgery using postoperative 5-fluorouracil had a 50% failure rate.³⁰ However, trabeculectomy with mitomycin-C has a better chance of success.³¹ These filters often fail due continued growth of the endothelial membrane over the internal ostium. This may be successfully treated with needling or by neodymium:yttrium-aluminum-garnet (Nd:YAG) laser application. Before a second trabeculectomy is done, needling should always be attempted. Eyes that fail a second trabeculectomy should undergo aqueous shunt implantation.³² One study has recommended the Ahmed valve in these eyes because the flow-restricting device may prevent postoperative shallow anterior chambers and further endothelial damage.³³ Contact cyclophotocoagulation with the diode laser or Nd:YAG laser may be necessary if the above procedures fail to control the intraocular pressure.

CORNEAL EDEMA

Reducing the intraocular pressure may occasionally also improve the corneal edema, although Wilson and Shields found no correlation between the presence and severity of

corneal edema and the level of IOP.²⁹ Often, even with lowered intraocular pressure, supplemental hypertonic saline may be necessary. Corneal transplantation is indicated for visual rehabilitation and relief of pain, and to provide clear media for careful monitoring of the optic disc and visual field. The prognosis for corneal transplant surgery is encouraging.³⁴

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ELEVATED EPISCLERAL VENOUS PRESSURE AND GLAUCOMA

Michael Passo, M.D.

Glaucomas associated with elevated episcleral venous pressure (EVP) are a diverse group of conditions, with increased pressure in the episcleral veins playing at least some role in the pathogenesis of the elevated intraocular pressure (IOP). Correct identification of this type of glaucoma is important because diagnosis of the underlying condition may require a multidisciplinary approach, and the most effective treatment is often directed at the primary etiology. Conventional medical glaucoma management may have limited benefit, and surgical complications, such as choroidal hemorrhage, are more common than with other forms of glaucoma. As our ability to diagnosis and treat the diverse underlying conditions continues to improve, so will our success in dealing with these unusual and sometimes treacherous forms of glaucoma.

BACKGROUND

Our understanding of the role of episcleral veins in aqueous humor dynamics started at the beginning of the 20th century with pioneering work by Lauber on the dilution of red blood cells in canine anterior ciliary veins.¹ This led to Seidel's observation in 1923 that India ink injected into the anterior chamber managed to gain access to the episcleral veins.² In 1942, Ascher made the first direct observation of the aqueous veins.^{1,3,4} We now know that episcleral veins are one of several ocular vascular beds that drain ultimately into the orbital veins and cavernous sinus (Table 23-1). These anatomic considerations are discussed and illustrated in Chapter 3.

TABLE 23-1 OCULAR VASCULAR BEDS DRAINED BY THE ORBITAL VEINS AND CAVERNOUS SINUS

Muscular Veins	Vortex Veins	Central Retinal Vein
Episcleral	Choroid	Retina
Aqueous	Ciliary body and iris	Optic nerve head
Schlemm's canal		Optic nerve

Decades of research have shown that, although EVP does influence IOP, it contributes little to the etiology of most forms of glaucoma. However, increased EVP from a diverse group of causes can be associated with elevated IOP and glaucomatous optic nerve damage.

PATHOGENESIS

Table 23-2 shows that the glaucomas associated with increased EVP can be divided into two broad, mechanistic categories: (1) those in which elevated EVP directly increases IOP; and (2) those in which increased EVP plays only a partial or indirect role in the rise of the eye

TABLE 23-2 CLASSIFICATION OF ELEVATED EPISCLERAL VENOUS PRESSURE GLAUCOMAS

Primarily Due to Elevated Episcleral Venous Pressure

Venous obstruction

- Superior vena cava syndrome
- Cavernous sinus thrombosis
- Jugular vein obstruction
- Phlebitis

Arteriovenous anomalies

- Direct carotid–cavernous sinus fistula
- Indirect (dural) carotid–cavernous sinus fistula
- Orbital varix

Idiopathic

Elevated Episcleral Venous Pressure Plays a Role

Venous obstruction

- Thyroid orbitopathy
- Retrobulbar tumors
- Pseudotumor
- Amyloidosis

Arteriovenous anomalies

- Sturge–Weber syndrome

pressure. Within each of these categories, elevated EVP can result from either venous obstruction or arteriovenous anomalies.

In the first group, in which increased IOP results directly from elevated EVP, venous obstruction can result from either extravascular or intravascular causes. Extravascular causes generally consist of mass lesions that compress the superior vena cava or jugular veins. Intravascular causes include cavernous vein thrombosis (both septic and aseptic) and phlebitis. The majority of arteriovenous anomalies are either direct or indirect carotid–cavernous sinus fistulas, or orbital varices.

Although IOP generally increases directly with the rise in EVP in these conditions, two rare exceptions exist. One occurs in carotid–cavernous sinus fistulas, which can elevate IOP through neovascular mechanisms secondary to reduced arterial flow.⁶ The other is acute angle closure from choroidal expansion induced by venous stasis.⁷

In the second group of disorders, elevated EVP is only partly responsible for the increased IOP. Among these conditions, the venous blockage and subsequent elevated eye pressure result from the mass effect of space occupying lesions within the orbit, such as thyroid orbitopathy. However, these lesions can also elevate IOP by direct pressure on the eye. In addition, eyes with significant proptosis can develop ocular surface problems, leading to exposure keratitis, intraocular inflammation, and increased eye pressure through uveitic mechanisms.

The arteriovenous abnormalities of the Sturge-Weber syndrome increase IOP through at least two possible mechanisms. These include anterior chamber anomalies, similar to those seen in congenital glaucoma, and a direct elevation of IOP due to episcleral and choroidal hemangiomas. Whereas glaucoma from the former typically begins in infancy, the latter mechanism usually produces glaucoma later in life.^{8–11}

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

General signs and symptoms of glaucoma associated with elevated EVP are local irritation, redness, and mattering with dilated and tortuous episcleral veins that do not blanch with topical vasoconstrictors. This can be easily confused with conjunctivitis. Other signs and symptoms are presented in Table 23–3. The differential diagnosis

TABLE 23-3 DIAGNOSIS OF ELEVATED EPISCLERAL VENOUS PRESSURE GLAUCOMAS

Symptoms	Signs
Local irritation and mattering	Dilated and tortuous episcleral vessels Chemosis
Pain	Proptosis
Diplopia	Blood in Schlemm's canal Restricted ocular motility Increased intraocular pressure

should also include episcleritis, scleritis, allergic conjunctivitis, orbital cellulitis, ocular pemphigoid, neovascular glaucoma, and any inflammatory process involving the anterior segment and orbit.

IOP should be measured in patients with thyroid orbitopathy with the eye in the “resting” position. This avoids falsely elevated measurements, due to altered scleral rigidity and muscular contraction.¹² Pneumotonometry can also be useful in measuring ocular pulse amplitude, which can be increased with carotid–cavernous sinus fistulas.¹³

PEARL... In patients with thyroid orbitopathy, the intraocular pressure should be measured with the eye in the “resting” position to avoid falsely elevated readings.

Diagnostic tests generally include imaging studies, such as ultrasound biomicroscopy,¹⁴ orbital ultrasonography (Fig. 23–1), computerized axial tomography, magnetic resonance imaging, and angiography. Appropriate consultations with a neuroophthalmologist, a neuroradiologist, and an orbital surgeon are often necessary to make the diagnosis and provide the proper treatment.

Specific clinical features of some of the more common disorders are described in the following text and presented in Table 23–4.

SUPERIOR VENA CAVA SYNDROME

Obstruction of the superior vena cava usually results from a malignancy in the upper thorax, although pulmonary hypertension may have a similar effect (Fig. 23–2A,B). The clinical picture is one of facial and orbital tissue congestion and cyanosis, including proptosis and increased IOP.¹⁵ These are made worse when the patient is recumbent.¹⁶

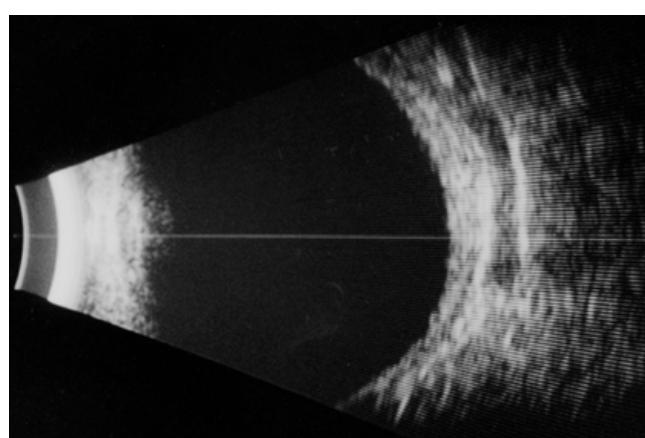


FIGURE 23-1 Orbital ultrasound demonstrating a dilated superior ophthalmic vein behind the globe.

TABLE 23-4 CLINICAL FEATURES OF MOST COMMON CAUSES OF ELEVATED EPISCLERAL VENOUS PRESSURE GLAUCOMA

Cause	Clinical Features
Superior vena cava syndrome	Exophthalmos Edema and cyanosis of face and neck
Cavernous sinus thrombosis	Patient may be septic Proptosis, lid edema, pain Ocular motor palsies Venous stasis retinopathy
Direct carotid–cavernous sinus fistula	History of trauma, acute onset, young age Chemosis, pulsating exophthalmos bruit Ocular motor nerve and muscle dysfunction Increased ocular pulse Venous stasis retinopathy, neovascularization
Indirect carotid–cavernous sinus fistula	No history of trauma, slow onset, older age Minimal proptosis Corkscrew dilated episcleral veins
Orbital varices	Intermittent exophthalmos Worse with Valsalva maneuver Often bilateral
Thyroid orbitopathy	Lid retraction and lag Proptosis Restricted ocular motility Exposure keratopathy
Sturge-Weber	Facial, conjunctival, episcleral hemangiomas Leptomeningeal angioma
Idiopathic	Prominent episcleral veins Rule out all other causes

CAVERNOUS SINUS THROMBOSIS

Cavernous sinus thrombosis usually presents with severe orbital disease, including pain, proptosis, and palsies of any combination of cranial nerves 3 through 6. When due

to infection, patients are usually septic and severely ill. The differential diagnosis includes the Tolosa-Hunt syndrome (idiopathic inflammation of the superior orbital fissure and anterior cavernous sinus).¹⁷

CAROTID–CAVERNOUS SINUS FISTULAS

Carotid–cavernous sinus fistulas can be either direct or indirect.^{18,19} Direct communication between the internal carotid artery and the cavernous sinus creates a “high flow” situation, with pulsating exophthalmos, an orbital bruit, and congestion capable of producing pain, diplopia (from compression and ocular motor palsies), and profound ocular ischemia. These patients tend to be young and often give a history of trauma, which can vary from trivial to severe.

By contrast, indirect, or dural, carotid–cavernous sinus fistulas tend to occur spontaneously. Because these lesions are fed by smaller, intracavernous branches of the internal and external carotid arteries, the rate of blood flow in them is much lower, with the slow development of corkscrew-like, dilated episcleral veins (Fig. 23–3A–C). The typical patient is older and female, often with a history of systemic hypertension and vascular disease. However, some cases present even in infancy and can rarely be associated with systemic hypertension and vascular disease, pregnancy, trauma, and connective tissue disease, such as Ehlers-Danlos.²⁰

Presenting mostly unilaterally, this condition is often subtle and can masquerade as chronic conjunctivitis. More severe cases can present similarly to direct carotid–cavernous sinus fistula patients. Retinal vascular engorgement can be striking, leading to papilledema and choroidal detachment (Fig. 23–4A,B).

ORBITAL VARIX

Orbital varices are usually bilateral and characteristically present with intermittent proptosis related to the Valsalva maneuver.^{21,22} Because symptoms are intermittent and

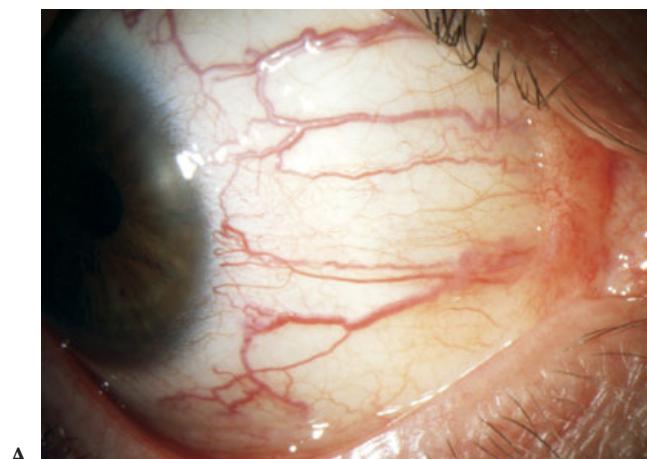
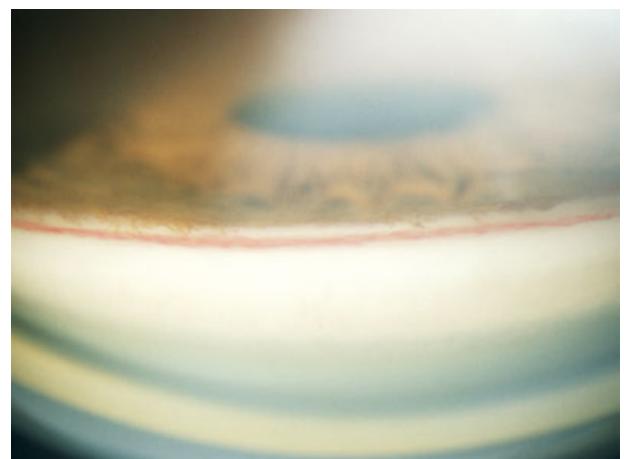


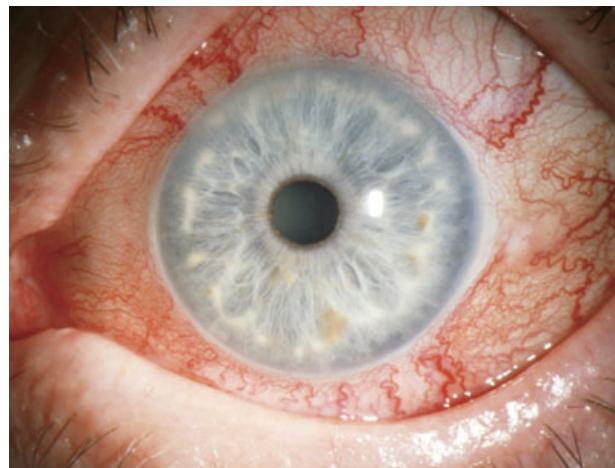
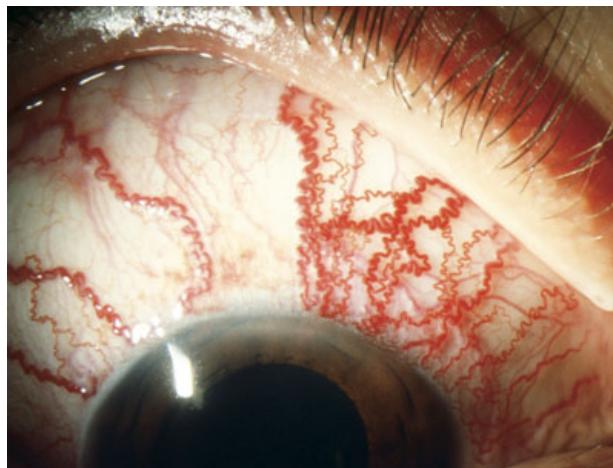
FIGURE 23-2 A patient with pulmonary hypertension and elevated IOP demonstrates (A) prominent episcleral veins and (B) blood in Schlemm's canal.



B



FIGURE 23-3 Indirect (dural) carotid–cavernous sinus fistula. (A) Unilateral injection may initially resemble a conjunctivitis. (B) Close inspection of the involved eye of another patient demonstrates the typical dilated, corkscrew vessels. (C) This image illustrates the spectrum of severity, as well as its sectoral nature.



varices may improve spontaneously, glaucomatous optic nerve damage is uncommon, and conservative management is usually successful.

THYROID ORBITOPATHY

Elevation of EVP in thyroid orbitopathy results from the lymphocytic infiltration of the extraocular muscles and resultant proptosis and venous congestion. This condition can increase IOP directly through external ocular compression, as well as through increased EVP. In extreme

cases, with corneal exposure and intraocular inflammation, increased eye pressure can result from inflammatory mechanisms.

Infiltration and contracture of the extraocular muscles can also restrict eye movement and affect IOP in a “gaze-dependent” fashion. For this reason, the examiner must remember to measure IOP with the eye in its “resting” position to avoid falsely increasing the pressure.¹² Other clinical features can include lid lag and retraction, chemosis, and extraocular muscle dysfunction. Recent studies suggest that a more serious orbitopathy can be

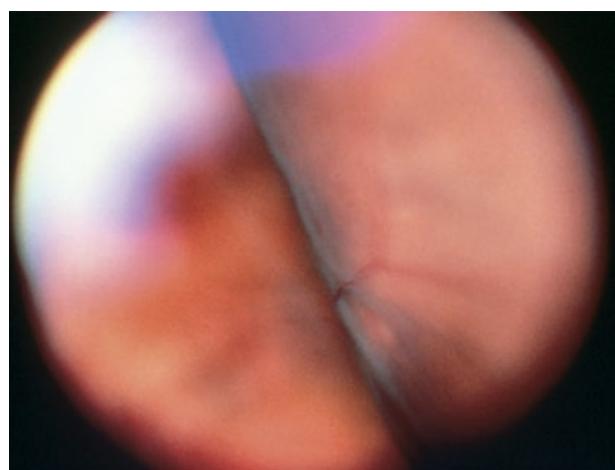
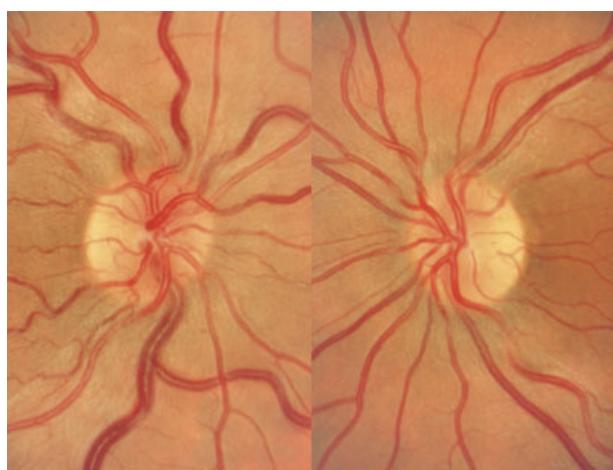


FIGURE 23-4 Retinal signs of severe, indirect, carotid–cavernous sinus fistula. (A) Engorged retinal vessels on the involved side (left plate) and (B) choroidal detachment.

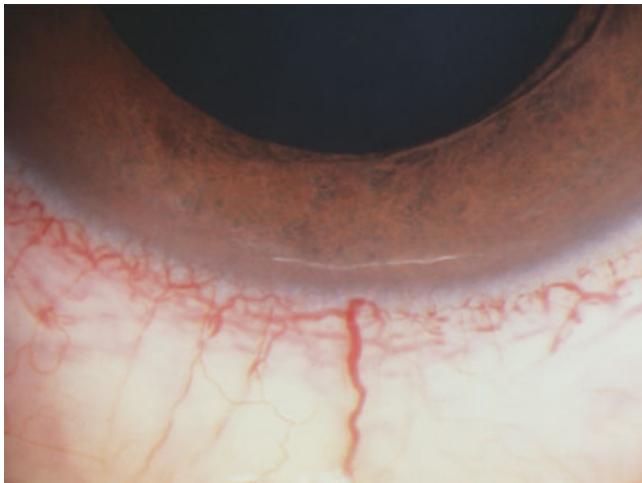


FIGURE 23-5 Tortuous limbal capillaries in Sturge-Weber syndrome.

associated with patients who smoke, whose thyroid functions are poorly controlled, and who have undergone radioiodine treatment for ocular disease prior to treatment.²³ This is also discussed and illustrated in Chapter 30.

PEARL... Patients who smoke, whose thyroid functions are poorly controlled, and who have a history of radioiodine treatment may develop a more serious orbitopathy.

STURGE-WEBER

Sturge-Weber is a systemic disease involving facial cutaneous and leptomeningeal angiomas. Glaucoma occurs in approximately 30 to 70% of patients and usually presents early in life due to anterior chamber anomalies similar to congenital glaucoma.^{8–11,24} There is also a late-onset glaucoma with clinical signs of raised EVP that results from arteriovenous shunts within episcleral hemangiomas. Many of these patients demonstrate irregular, telangiectatic limbal capillaries, in addition to dilated episcleral veins (Fig. 23–5). Glaucoma associated with Sturge-Weber is also discussed and illustrated in Chapter 30.

IDIOPATHIC ELEVATED EPISCLERAL VENOUS PRESSURE

Idiopathic cases of glaucoma associated with elevated EVP have been reported in both sporadic and familial occurrences.^{25–27} Most cases are unilateral and the associated glaucoma can be severe. These patients demonstrate typically dilated episcleral veins (Fig. 23–6), but lack the signs of the known causes of elevated EVP (Table 23–4), making this a diagnosis of exclusion. Whether these are truly idiopathic or perhaps low flow carotid–cavernous sinus fistulas that are difficult to demonstrate remains to be seen.

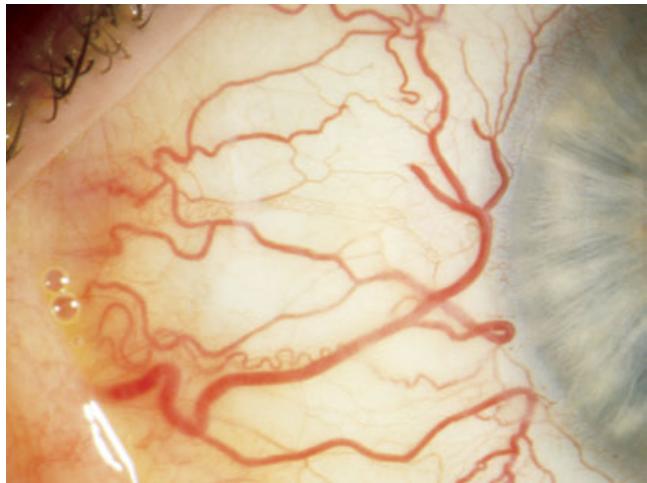


FIGURE 23-6 Idiopathic prominent episcleral veins.

CONTROVERSY

It is unknown whether patients with idiopathic elevated episcleral venous pressure are truly idiopathic, or simply have low flow carotid–cavernous sinus fistulas that are difficult to demonstrate.

MEDICAL AND SURGICAL MANAGEMENT

Many of the conditions that give rise to elevated EVP have specific, often neuro-ophthalmologic causes. Therefore, the most effective glaucoma management often relies on specific management of the underlying problem. In other instances, or when pressure must be controlled while waiting for these interventions to act, IOP can be treated with topical, and occasionally, oral aqueous suppressants. Surgery, when necessary, carries an increased risk of complications following sudden decompression of the globe, and may require specific measures before and after surgery.

PITFALL... Glaucomas associated with elevated episcleral venous pressure often resist conventional medical glaucoma management and they are more likely to suffer surgical complications, such as choroidal hemorrhage.

Whenever possible, management should address the underlying problem. This is particularly true when the etiology is due to venous obstruction from mass effect (thyroid orbitopathy, retrobulbar tumors, pseudotumor, superior vena cava syndrome, jugular vein thrombosis) or infection (cavernous sinus thrombosis, phlebitis).

Arteriovenous anomalies (carotid cavernous sinus fistulas, orbital varices) may also be treated primarily with intravascular embolization and balloon occlusion. Newer techniques using transvenous approaches have proved to be successful in up to 97% of cases with carotid–cavernous sinus fistulas.^{19,28}

Although these methods are very promising, they carry significant risks for cerebral and ocular ischemia, which must be considered carefully before a surgical approach is taken. This can be especially true in patients with compromised vessels due to vascular disease or Ehlers–Danlos syndrome.²⁹ Some cases will respond best to a conservative approach, especially with low flow dural carotid–cavernous sinus fistulas, where the glaucoma is often not visually threatening and over half of patients can spontaneously close or improve.³⁰ Improvement has also been reported following angiography.^{31,32}

Medical management in elevated EVP glaucomas will not generally reduce eye pressure below that within the episcleral veins, but it is always worth trying. Often, the goal of therapy is only normalization of the IOP, or perhaps temporary reduction until definitive therapy or spontaneous improvement can intervene. Some of these patients may also have coexistent primary open-angle glaucoma, which could be responsive to the usual management strategies.

SPECIAL CONSIDERATION

Some patients with elevated episcleral venous pressure may also have coexistent primary open-angle glaucoma, which may respond well to glaucoma medications.

Aqueous suppression with beta-adrenergic antagonists, carbonic anhydrase inhibitors, and alpha-2 agonists can reduce IOP in some of these eyes. Because efficacy may be less likely, a one-eye trial in bilateral cases can help the clinician identify the most useful agent. Another useful tool is an expedited therapeutic trial, with one drop of test medication to the eye, punctal occlusion, and repeat IOP measurement 2 hours later.

Pilocarpine and prostaglandin analogs are generally not effective, except in the juvenile form of glaucoma in the Sturge–Weber syndrome. Treatment with latanoprost may also be associated with an increase in episcleral venous engorgement, which could possibly increase the risk of postoperative complications.³³

Laser trabeculoplasty may also be tried, but clinical reports suggest it is unlikely to be successful. However, panretinal photocoagulation is a useful adjunctive treatment for neovascular glaucoma associated with carotid–cavernous sinus fistulas.³⁴

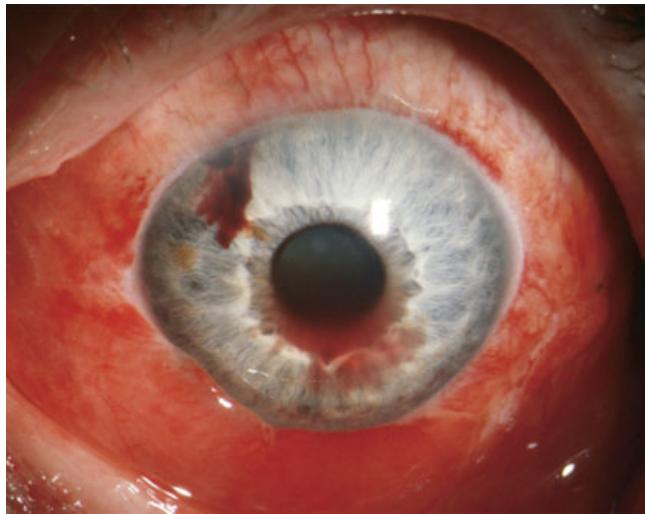


FIGURE 23-7 Patient with a carotid–cavernous sinus fistula following a trabeculectomy. Note intraocular hemorrhage and shallow anterior chamber. The patient later developed a large choroidal detachment.

Filtering surgery remains the treatment of choice for many of these cases. However, the elevated venous pressure may increase the potential for complications, such as intraoperative and postoperative choroidal effusion and hemorrhage (Fig. 23-7). Although a guarded trabeculectomy is the gold standard, other procedures, such as placement of an aqueous shunt or a nonpenetrating surgery, may be considered in specific cases. When placing an aqueous shunt, the surgeon should use a valved device or a tube ligature to reduce postoperative hypotony. All of these devices are contraindicated in cases with severe orbital congestion and proptosis, due to space limitations. Although nonpenetrating procedures may help minimize sudden decompression in some of these eyes, the use of these techniques awaits further experience.^{35,36}

Regardless of the procedure selected, the surgeon must avoid rapid decompression of these eyes at the time of surgery. Viscoelastics to maintain the anterior chamber, and pre-placed, snug, releasable suture techniques can all help reduce sudden changes in IOP. Antimetabolites can enhance the efficacy of the procedure and allow for greater flexibility in the timing of suture lysis. However, they can also increase the risk of hypotony, and their use should be decided on a case-by-case basis. High-risk cases, such as in Sturge–Weber syndrome, may be best managed with prophylactic sclerotomies at the time of filtration surgery. Early onset Sturge–Weber cases may require a trabeculotomy or goniotomy.

Anesthetic considerations include general anesthesia and local, retrobulbar injection. If the surgeon is comfortable with topical anesthesia, this may be the safest approach to reduce bleeding and decrease the potential for retrobulbar hemorrhage in these high-risk eyes.

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OCULAR TRAUMA, HEMORRHAGE, AND GLAUCOMA

Scott Elliot LaBorwit, M.D.

Ocular trauma can increase the resistance to aqueous outflow and produce glaucoma by obstructing or damaging the trabecular meshwork through a variety of mechanisms. Determining if the original injury is nonpenetrating or penetrating provides a useful clinical differentiation, pointing the clinician to several distinct entities. Nonpenetrating trauma, or ocular contusion, can produce glaucoma through inflammation and intraocular hemorrhage, as well as injury to the lens. Depending on the specific entity, these glaucomas can develop by either open-angle or closed-angle mechanisms and the rise in intraocular pressure (IOP) may occur acutely or develop long after the original injury. Penetrating ocular injuries present additional mechanisms of glaucoma, such as epithelial downgrowth and the possibility of retained intraocular foreign bodies.

Following trauma, a comprehensive evaluation, including a thorough history and examination, is necessary to determine which mechanisms have caused, or may potentially cause, glaucoma. The physician must always remember that traumatic glaucoma can be complicated by the early and late presentation of high IOP, as well as other serious ocular complications, such as cataracts, corneal perforations, and retinal pathology. A thorough understanding of these entities and their management is crucial to the successful management of these challenging and diverse forms of glaucoma.

EPIDEMIOLOGY OF TRAUMA

According to population-based surveys, the incidence of medically treated ocular injuries in urban America ranges from 1.8 to 5.6 per thousand per year for individuals 40 years of age and above.¹ The annual incidence of ocular trauma requiring in-patient hospital treatment for the same population is 13.2 per 100,000 per year.²

Both hospital-based studies and population-based studies reveal differences in the demographics of persons with ocular injuries. Seventy to 85% of ocular injuries, superficial and severe, occur in males.^{3–5} The Baltimore Eye Survey showed that the prevalence of visual impairment and blindness due to trauma among African American men is three to four times higher than among white men.¹

With regard to age, ocular trauma occurs in a bimodal distribution, with the maximal risk occurring in young adults and in persons 70 years of age and above.³ Falls constitute the leading cause of open-globe trauma in the elderly,^{1,2} whereas motor vehicle accidents, occupational trauma, and assault are the most common etiologies of severe eye injury among young adults.^{1,6} For children, domestic accidents, play, or organized sports account for more than 70% of open-globe injuries.⁷

NONPENETRATING INJURIES (OCULAR CONTUSION) (TABLE 24-1)

INFLAMMATION

Anterior chamber inflammation is a common complication of trauma and can produce glaucoma through a variety of mechanisms. Initially, the IOP may vary widely. Swelling of the ciliary body may decrease aqueous production, leading to low IOP. Subsequent recovery of aqueous humor formation can be associated with a secondary open-angle glaucoma due to obstruction of the trabecular meshwork by inflammatory cells, protein, or other serum components liberated with disruption of the blood-aqueous barrier.⁸

Inflammation within the trabecular meshwork obstructs outflow by several additional mechanisms, including meshwork swelling, endothelial cell damage, or membrane formation.^{9,10} Secondary closed-angle glaucoma

TABLE 24-1 GLAUCOMA FOLLOWING NONPENETRATING OCULAR TRAUMA

Cause	Mechanism	Presentation
Inflammation	TM obstruction with WBC and protein	Early; open-angle
	Direct TM inflammation	Early; open-angle
	PAS	Late; closed-angle
	Pupillary block	Early or late; closed-angle
	Neovascular glaucoma	Late; closed-angle
	Ciliary body swelling	Early; closed-angle
Hemorrhage/hyphema	TM obstruction with RBC and fibrin	Early; open-angle
	Pupillary block from clot in anterior chamber	Early; closed-angle
Ghost cell glaucoma	TM obstruction with degenerated RBC membranes	Weeks; open-angle
Hemolytic glaucoma	TM obstruction with macrophages	Weeks; open-angle
Hemosiderotic glaucoma	Siderosis of TM endothelium	Late; open-angle
Angle recession	TM atrophy and sclerosis	Late; apparently open-angle
	Descemetization	
Lens subluxation and/or dislocation	Pupillary block	Early or late; closed-angle
	Direct angle obstruction	
Traumatic cataract	Pupillary block	Early or late; closed-angle
	Direct angle obstruction	
Phacolytic glaucoma (mature cataract)	TM obstruction with macrophages	Late; open-angle
Lens particle glaucoma	TM obstruction with lens material	Early or late; open-angle
Forward displacement of lens-iris diaphragm	Pupillary block	Early; closed-angle
	Angle compression	

PAS, peripheral anterior synechiae; TM, trabecular meshwork; RBC, red blood cells; WBC, white blood cells.

results when the outflow is compromised by peripheral anterior synechiae (PAS), pupillary block from posterior synechiae (iris bombé), neovascular glaucoma, ciliary body swelling, or anterior rotation of the ciliary body due to uveal effusion (Fig. 24-1A,B).¹¹

PEARL... Although inflammation following ocular trauma may initially produce hypotony, subsequent recovery of aqueous humor formation can result in open- and closed-angle forms of glaucoma.

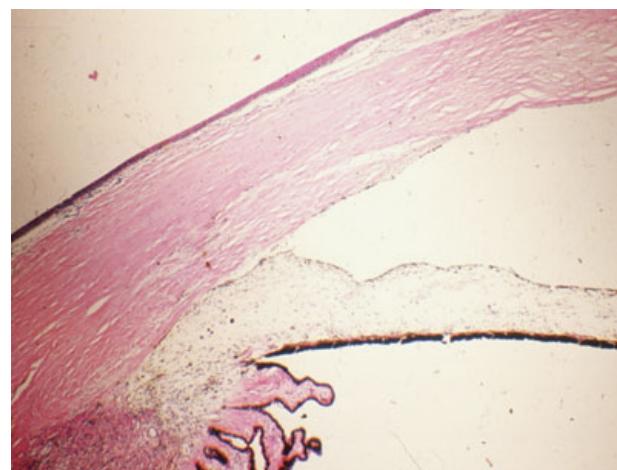
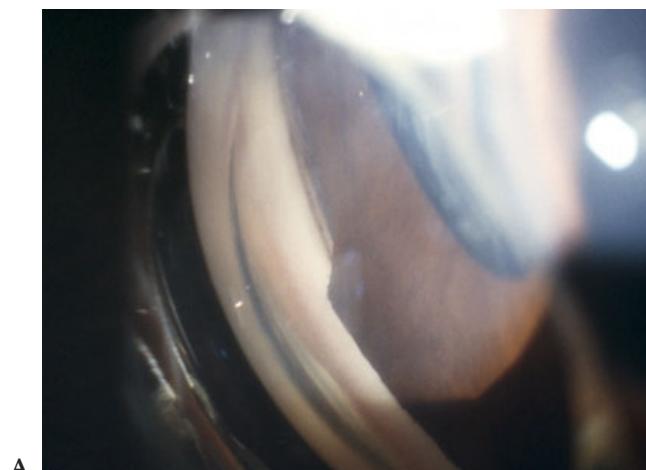


FIGURE 24-1 (A) Broad-based peripheral anterior synechiae resulting from inflammation following trauma covering a portion of the trabecular meshwork, leaving a portion of the angle open. (B) Histopathology of PAS following ocular contusion. (Figure 24-1B courtesy of W. Richard Green, M.D.)

Diagnosis of glaucoma due to inflammation is made by slit-lamp visualization of the inflammatory cells and flare within the anterior chamber. The anterior chamber angle must be examined by gonioscopy to determine if the angle is open or closed and to identify any evidence of PAS or angle neovascularization.

Medical treatment of glaucoma is directed toward controlling inflammation and lowering the IOP. Cycloplegic agents can prevent and break posterior synechiae and prevent iris bombé and can also be used to reverse anterior rotation of the ciliary body. Topical, subconjunctival, or parenteral corticosteroids will suppress the inflammatory response, although their long-term use should be tempered by the possibility of producing steroid-induced glaucoma.¹²

Aqueous humor suppressants are the most appropriate medications for controlling IOP. Latanoprost¹³ and pilocarpine^{14,15} may be contraindicated because they can increase anterior chamber inflammation. Miotics may also predispose to posterior synechiae in the presence of inflammation.

Argon laser trabeculoplasty (ALT) is generally ineffective in eyes with a history of inflammatory or uveitic glaucoma.¹⁶ A laser iridotomy is necessary, however, when advanced posterior synechiae can or do lead to pupillary block (iris bombé).

Eyes that do not respond to medical management will require surgery. This typically involves a trabeculectomy combined with antifibrosis agents to increase the likelihood of success. A valve implantation or cyclophotocoagulation is performed when a trabeculectomy fails.

HYPHEMA

A hyphema may result from both nonpenetrating and penetrating ocular injury. In nonpenetrating blunt injuries, the majority of hyphemas result from sports injuries and assaults.¹⁷ The incidence of hyphema ranges from 6% for pediatric patients with ocular trauma¹⁸ to 55% in a survey of penetrating injuries caused by assault.¹⁹

Pathogenesis

Blunt impact to the front of the eye rapidly increases IOP, causing equatorial expansion of the globe and posterior displacement of the lens-iris diaphragm. The resulting shearing forces may lead to a direct rupture of the iris and ciliary body vessels and an acute hyphema. In addition, a tear in the anterior face of the ciliary body may disrupt the major arterial circle of the iris.

A serious complication of hyphemas is rebleeding, generally due to clot retraction and lysis 2 to 5 days after the initial injury.²⁰ The reported incidence varies between 5 and 33%.^{21,22} These rebleeding episodes are associated with more complications than occur with the initial hyphema. These include glaucoma, corneal blood staining, and vitreous hemorrhage.²²

Following a hyphema, the IOP may become acutely elevated by mechanical obstruction of the trabecular meshwork with erythrocytes and blood products. Total or large hyphemas, as may occur with rebleeding, may cause pupillary block and contribute to elevated IOP. Although fresh erythrocytes readily escape the anterior chamber, excessive amounts of red blood cells, plasma, fibrin, and debris may overwhelm the meshwork. This can lead to an acute but transient obstruction, which may nevertheless cause glaucomatous optic neuropathy. Persistent glaucoma occurs in only 1% of patients with hyphema following blunt injury.¹⁷ However, prolonged IOP elevation with hyphema may cause corneal blood staining, resulting in amblyopia in younger patients.

Patients with sickle cell trait and disease are more susceptible to complications from a hyphema. The sickle deformity of these red blood cells makes it more difficult for them to pass through the trabecular meshwork. Because of this, even small amounts of blood in the anterior chamber can produce a severe elevation of the IOP.²³ The sickling deformity also causes suboptimal blood flow within the optic nerve head, contributing to optic atrophy at only slightly elevated IOPs.^{23,24} This condition also is discussed in Chapter 30.

Diagnosis

The diagnosis of hyphema depends on the slit-lamp observation of layered blood in the inferior chamber angle (Fig. 24–2A,B). The incidence of elevated IOP is correlated to the size of the hemorrhage, which can be graded by its height in millimeters.²⁵ Careful evaluation after trauma may reveal circulating red blood cells in the anterior chamber without layering, often called a microscopic hyphema. Daily evaluation is necessary to detect any evidence of a recurrent hemorrhage, such as an increase in the size of the hyphema and brighter-colored red blood cells. Gonioscopic evaluation is best deferred for several days to avoid disturbing any clots and precipitating a recurrent hemorrhage.

Management

The goals of hyphema treatment are to accelerate blood resorption, reduce the risk of secondary hemorrhage, and control IOP elevations, as necessary. However, the recommendations for accomplishing these goals are variable and controversial due to lack of a universally accepted treatment. Therefore, the clinician must choose the proper management for each patient based on the severity of injury, age, maturity, and other risk factors.

Hospitalization with activity restriction and close observation has not been proven to prevent rebleeding.²⁰ It may, however, be recommended for patients requiring close IOP monitoring.

It is helpful to shield the injured eye to prevent accidental trauma while cycloplegia is also used to paralyze

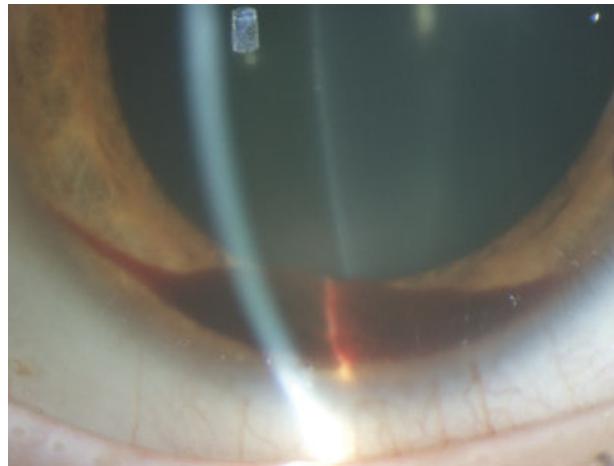
**A****B**

FIGURE 24-2 (A) Patient with anterior chamber hemorrhage following an automobile airbag injury. Note blood clot and early layered hyphema. Marked corneal edema and large iridodialysis also indicate a severe contusion injury. (B) Layered, resolving hyphema. The dark color is consistent with old blood.

the ciliary body and limit iris movement around the clot.^{20,26} In the past, biomicroscopy and tonometry were recommended every 6 to 12 hours to detect possible complications. However, in the outpatient setting, daily examination is more practical.

Aminocaproic acid (Amicar) reduces the incidence of secondary bleeding by stabilizing the clot.²⁷ The recommended dose is 50 mg/kg every 4 hours and should not exceed 30 g per day. However, side effects of nausea, vomiting, and postural hypotension, and the potential for deep vein thrombosis along with the high cost of the medication, force the clinician to weigh the risks and benefits of this medication in each case. One study has shown that topical aminocaproic acid is as effective as the oral route.²⁸ An alternative is oral Prednisone, 0.6 mg/kg every day, which can reduce rebleeding to an extent comparable to that of oral Amicar.²⁹ Aspirin and other drugs that interfere with the clotting mechanism are contraindicated.

CONTROVERSY

Although aminocaproic acid can decrease the incidence of secondary hemorrhage following a traumatic hyphema, side effects and cost generally limit its use to a case-by-case basis.

Topical corticosteroids help reduce anterior chamber inflammation. IOP elevation should be controlled using topical glaucoma medication. However, epinephrine may increase inflammation and should be avoided, as should miotics due to their effects on the ciliary body. Oral and intravenous hyperosmotic agents may be used in cases

with persistent IOP elevation and where the patient has no contraindication such as congestive heart failure or hemoglobinopathy.

African American patients with a hyphema should routinely have immediate sickle cell screening. In patients with sickle cell trait or disease, the average IOP over each 24 hours should not exceed 24 mm Hg due to the increased risk of optic atrophy after even mild pressure increases.³⁰ In addition, systemic agents such as acetazolamide or methazolamide must be used with caution because of the risk of anterior chamber acidosis, which can increase erythrocyte sickling. These medications also contribute to hemoconcentration and vascular sludging. When necessary, methazolamide is the more desirable choice because it produces a less profound systemic acidosis.³¹

Occasionally, it becomes necessary to remove anterior chamber blood to avoid optic nerve atrophy. Severe persistent pressure elevation, corneal blood staining, or high risks of PAS are indications for surgical intervention. An average pressure of more than 50 mm Hg for 5 days or 35 mm Hg for 7 days is a suggested guideline for surgical intervention to prevent optic atrophy in patients without sickle cell trait or disease (Table 24-2).³² Clinical evidence of corneal blood staining occurs when granular deposits appear in the posterior stroma of the cornea, and this is an urgent indication for surgical removal of the hyphema.

TABLE 24-2 GUIDELINES OF MAXIMUM TOLERATED IOP TO PREVENT OPTIC ATROPHY IN PATIENTS WITH HYPHEMAS

Average Pressure (mm Hg)	Duration (days)	Sickle Cell Prep
50	5	Negative
35	7	Negative
24	1	Positive

and anterior chamber washout. Total hyphemas persisting for more than 5 days, or diffuse hyphemas involving most of the anterior chamber persisting for more than 9 days, significantly increase the risk of PAS.³²

Surgical removal of anterior chamber blood may be performed by either expression of the clot through a shelved limbal incision or anterior chamber washout using an irrigation cannula and a vitreous cutting instrument, as necessary.

GHOST CELL GLAUCOMA

Pathophysiology

Campbell et al first described elevated IOP caused primarily by degenerated red blood cells migrating forward from the vitreous.³³ They showed that, following a vitreous hemorrhage, the red blood cells degenerate and become more rigid within 1 to 2 weeks. The intracellular hemoglobin leaves the cells and precipitates extracellularly as large clumps that become adherent to vitreous strands.³⁴ Over time, macrophages gradually ingest these degenerated ghost cells and extracellular hemoglobin. However, an event that disrupts the anterior hyaloid face, such as trauma or intraocular surgery, may allow these ghost cells to migrate into the anterior chamber.

The mechanism of IOP elevation is due to obstruction of aqueous outflow. Ghost cells are less pliable than fresh erythrocytes and cause severe obstruction of the inter trabecular spaces.³⁵ Campbell reviewed 14 patients with traumatic ghost cell glaucoma, and the IOP elevation occurred most commonly 1 month after the injury, with the IOP typically in the range of 30 to 50 mm Hg.³⁶

Ghost cell glaucoma depends on the combination of a vitreous hemorrhage and a violation of the anterior hyaloid face. In addition to trauma, vitreous hemorrhage can result from neovascularization due to retinal disease, and a defect in the anterior hyaloid face may occur following a complicated cataract extraction.

PEARL... Ghost cell glaucoma depends on the combination of a vitreous hemorrhage and rupture of the anterior hyaloid face.

Diagnosis

Slit-lamp examination reveals characteristic khaki-colored ghost cells in the anterior chamber. On gonioscopy, the angle appears open, covered by khaki-colored cells, especially inferiorly. These cells may layer in the inferior angle, forming a pseudohypopion, occasionally intermixed with a layer of fresh erythrocytes (Fig. 24-3).

Although the diagnosis is usually based on the history and clinical evaluation, a paracentesis and cytological examination can confirm the diagnosis in questionable

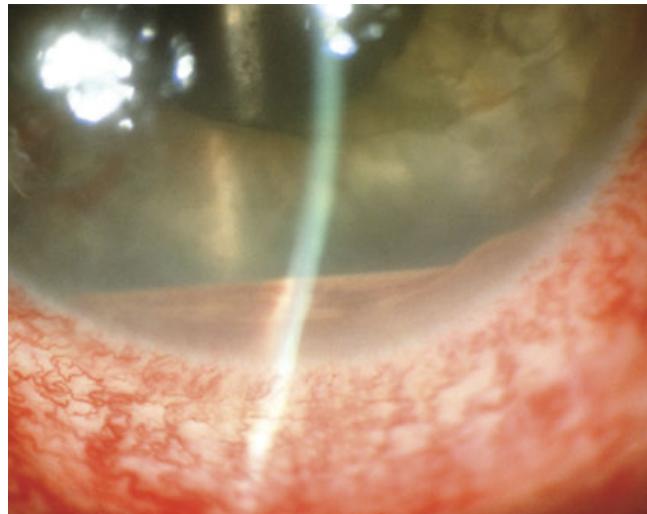


FIGURE 24-3 Ghost cell glaucoma, with layered, khaki-colored ghost cells intermingled with fresh red erythrocytes. (Courtesy of Julia Whiteside, M.D.)

cases. Ghost cells are best seen by wet preparation with phase-contrast microscopy. The cells appear spherical in shape and are empty except for clumps of degenerated hemoglobin, or Heinz bodies, that are adherent to the inner wall of the cell.³⁶

Management

The elevation of pressure is usually transient, but it may last for months as the rigid erythrocytes slowly clear from the anterior chamber angle. Treatment with standard antiglaucoma medical therapy includes beta-blockers, alpha agonists, and carbonic anhydrase inhibitors. Campbell found that fewer than half of his cases responded to medical therapy alone.³⁶ Cases refractory to medical management may require anterior chamber washout and, if this fails, pars plana vitrectomy to ensure complete removal of all blood components.

HEMOLYTIC GLAUCOMA

Hemolytic glaucoma occurs days to weeks after a large intraocular hemorrhage. The mechanism of IOP elevation is an obstruction of the trabecular meshwork by macrophages laden with pigment, erythrocytes, and debris.³⁷

Slit-lamp examination reveals reddish-brown cells in the aqueous humor, and gonioscopy shows an open angle with the trabecular meshwork covered with reddish-brown pigment. Cytological evaluation of the aqueous shows macrophages containing golden-brown pigment (Fig. 24-4).

Hemolytic glaucoma is a self-limited condition that usually responds to medical management. Recalcitrant cases may require surgical intervention such as anterior chamber washout.

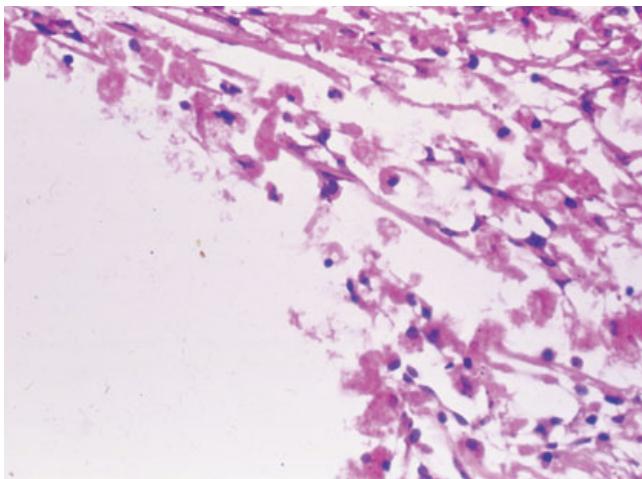


FIGURE 24-4 Histopathology of hemolytic glaucoma shows large macrophages containing erythrocyte debris throughout the trabecular meshwork. (Courtesy of Richard W. Green, M.D.)

HEMOSIDEROTIC GLAUCOMA

In this condition, elevation of pressure is related to the hemoglobin released from degenerated erythrocytes, which are phagocytized by endothelial cells of the trabecular meshwork after a long-standing intraocular hemorrhage. The iron in the hemoglobin may cause siderosis of the trabecular meshwork, although the mechanism is unclear for this rare condition.³⁸

ANGLE-RECESSSION GLAUCOMA

Angle recession is one of several anterior segment abnormalities that can result from blunt ocular trauma. The lateral, shearing aqueous forces that produce bleeding can also rupture the delicate relationships between the ciliary

muscle layers. This produces a cleft in the ciliary body band, or recession of the anterior chamber angle (Fig. 24-5A,B).

Sixty to 94 percent of patients with blunt ocular trauma have some degree of either angle recession or trabecular meshwork damage.^{21,39-42} Fortunately glaucoma is uncommon and occurs in 7 to 9% of eyes followed for 10 or more years.^{42,43} The duration from the initial injury and onset of elevated IOP ranges from 7.6 to 64 years.^{44,45} Occasionally, elevation of IOP may occur after a couple of months.⁴⁵

Pathophysiology

In 1892, Collins first described the pathology of angle recession resulting from blunt trauma to the eye.⁴⁶ It was not until 1962, however, that Wolff and Zimmerman unified the pathologic entity of angle recession with the clinical phenomenon of unilateral chronic glaucoma following trauma.⁴⁷

It is suggested that angle recession is only a marker of past trauma, and that the glaucoma results from injury to the trabecular meshwork. This stimulates degeneration or proliferative changes in the trabecular tissue,⁴⁷ leading to atrophy and sclerosis of the trabecular meshwork and compromised aqueous humor outflow. Reese proposed another mechanism, involving the formation of a membrane over the trabecular meshwork.⁴⁸ This hyaline membrane, sometimes referred to as Descemetization, is continuous with Descemet's membrane and extends over the iridocorneal angle, covering the trabecular meshwork. In addition, Tesluk and Spaeth have shown that patients with unilateral angle cleavage glaucoma have a 50% chance of developing open-angle glaucoma in the fellow eye.⁴⁵ This suggests that patients with traumatic angle recession who develop glaucoma are predisposed to develop bilateral chronic open-angle glaucoma.

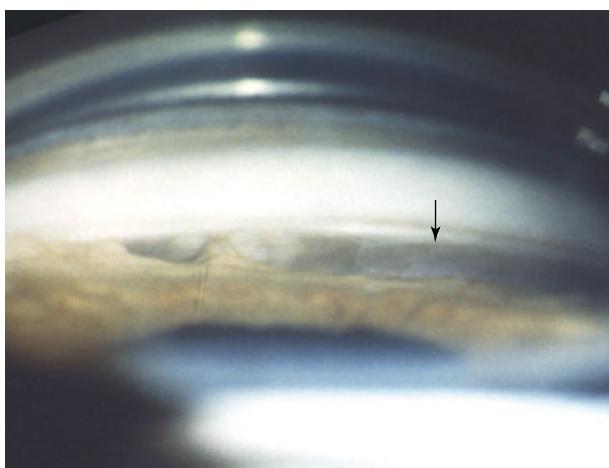
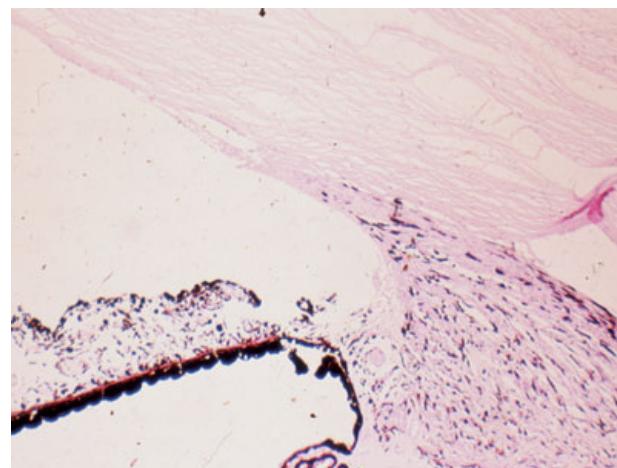


FIGURE 24-5 (A) Goniophotograph of angle recession due to blunt trauma from an automobile airbag shows deepening of angle with an abnormally white-appearing scleral spur. This eye also has faint gray-white membrane seen covering the angle (arrow). (B) Histologic appearance of an eye with angle recession and glaucoma after blunt trauma.



B

SPECIAL CONSIDERATION

A patient with angle recession who develops glaucoma has a 50% chance of developing glaucoma in the nontraumatized fellow eye.

Diagnosis

Gonioscopically, angle recession produces a deep angle with an abnormally wide ciliary body face. The scleral spur is prominent and may appear abnormally white, due to stripping away of the uveoscleral meshwork by the initial trauma. A gray-white membrane may occasionally extend from Descemet's in the cornea over the irido-corneal angle (Fig. 24-5A).^{47,48}

Recognizing angle recession is often difficult, due to wide variations in the contour and pigmentation of the normal angle. Because of this, the physician must have a high degree of suspicion for this condition to make the proper diagnosis. This is aided by the history of trauma and the presence of other signs of past trauma, such as lid or facial scars, an excessively deep anterior chamber or ante-

rior chamber asymmetry, iridodialysis, iridoschisis, iridodonesis, irregular angle pigmentation, phacodonesis, Vossius' ring (imprinting of posterior iris pigment on the anterior lens capsule by severe blunt trauma), and pupillary sphincter tears (Fig. 24-6A–C). The clinician should always consider trauma as a possible mechanism of elevated IOP in every patient with unilateral glaucoma.

Another consequence of ocular trauma, cyclodialysis, involves complete separation of the ciliary body from the scleral spur and sclera (Fig. 24-7). This typically produces ocular hypotony, although spontaneous closure can result in marked pressure elevation.

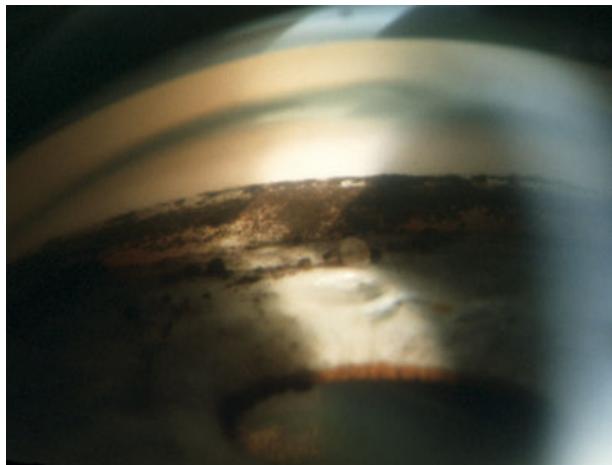
PEARL... The clinician should always consider trauma as a possible mechanism of elevated intraocular pressure in every patient with unilateral glaucoma.

Management

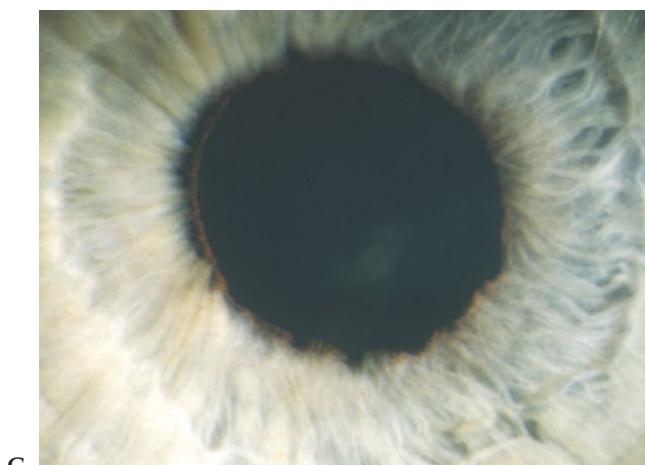
Standard medical glaucoma therapy generally constitutes initial pressure treatment, although efficacy is limited. Pilocarpine may cause a paradoxical increase in IOP in



A



B



C

FIGURE 24-6 Other anterior segment signs of past ocular trauma include (A) iridodialysis, (B) irregular angle pigmentation, and (C) subtle tears in the pupillary sphincter.

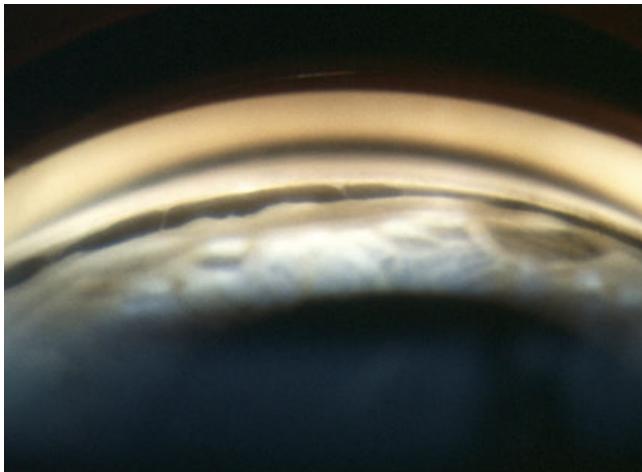


FIGURE 24-7 A broad cyclodialysis cleft, showing remnants of uveal attachments to a “bone white” scleral spur. The bottom of the cleft cannot be visualized, in contrast to angle recession.

eyes that are dependent on uveoscleral outflow as the predominant mechanism of outflow.⁴⁹ Laser trabeculoplasty is generally unsuccessful, with one series of 13 patients reporting a 36-month life-table success rate of 23%.^{50,51}

Filtering procedures are less successful in patients with angle recession compared with patients with chronic open-angle glaucoma, possibly due to excessive scarring of the conjunctiva by the initial trauma or prior surgical interventions. Mermoud et al showed that angle recession is an independent risk factor for filtering success, with 3-year success rates of 32% in the angle recession group versus 84% in the matched chronic open-angle group.⁵² However, mitomycin-C can increase the success rate of initial trabeculectomy in angle recession glaucoma from 26 to 58% at 2 years.⁵³

LENS-INDUCED GLAUCOMA

Damage to the crystalline lens, lens capsule, or zonules may induce either open- or closed-angle glaucoma. The major types of traumatic, lens-induced glaucoma include lens subluxation or dislocation, lens swelling with cataract formation, phacolytic glaucoma, and lens particle glaucoma. These entities are fully described and illustrated in Chapter 25.

FORWARD DISPLACEMENT OF THE LENS-IRIS DIAPHRAGM

Blunt trauma can occasionally induce a secondary angle-closure glaucoma that results from rotation of the ciliary body with forward displacement of the lens-iris diaphragm. Generally due to suprachoroidal effusion, hemorrhage, or ciliary body edema, this condition may be difficult to distinguish from lens subluxation or pupillary block. Slit-lamp examination reveals shallowing of both the central and peripheral anterior chamber. Indirect ophthalmoscopy gen-

erally will reveal a choroidal detachment, which can be distinguished from hemorrhage by ultrasonography.

The condition usually responds over time to treatment with cycloplegics and topical corticosteroids, and conventional topical, and occasionally oral, glaucoma therapy. Miotics may increase anterior chamber shallowing and are contraindicated. A peripheral iridotomy is not indicated because there is no pupillary block component.

PENETRATING OCULAR INJURIES

The incidence of penetrating ocular injuries (Table 24-3) varies from 94.3 per million persons for 10- to 19-year-old males to 3.9 per million persons for 60- to 69-year-old women.⁵⁴ The median age reporting to the National Eye Trauma System (NETS) is 28 years. Patients with assault-related injuries are 97% male.⁹ Among occupational penetrating injuries, the average age is 30, and 83% are males.⁵⁴ Intraocular foreign bodies were present in 6% of the assault-related injuries and 35% of the occupational injuries in patients reported to the NETS.^{10,55} The prognosis for vision after penetrating injury is poor, with only 25% of cases achieving 20/40 or better acuity, in one series.⁵⁶

GLAUCOMA WITHOUT RETAINED FOREIGN BODY

Pathophysiology

Penetrating trauma can produce outflow obstruction and elevated IOP through several mechanisms. Most commonly, a prolonged flat anterior chamber combined with inflammation leads to formation of permanent PAS. Alternatively, pupillary block and angle-closure glaucoma can result from posterior synechiae. Sympathetic ophthalmia,

TABLE 24-3 GLAUCOMA FOLLOWING PENETRATING OCULAR TRAUMA

Cause	Mechanism
Inflammation/anterior chamber collapse	TM obstruction PAS formation Pupillary block
Hemorrhage	Hyphema Ghost cell glaucoma Hemolytic glaucoma Hemosiderotic glaucoma Phacolytic glaucoma
Lens damage	Lens particle glaucoma Lens swelling (phacomorphic glaucoma)
Epithelial downgrowth	Angle obstruction and closure by epithelium
Siderosis	TM endothelial toxicity from iron
Chalcosis	Potential copper toxicity

PAS, peripheral anterior synechiae; TM, trabecular meshwork.

although rare, may lead to chronic inflammation in the fellow eye and induce a pressure elevation.⁵⁷

Intraocular hemorrhage, another common accompaniment of penetrating ocular injuries, can produce IOP elevation through hyphema, ghost cell glaucoma, hemolytic glaucoma, and hemosiderotic glaucoma. Violation of the lens capsule may result in either phacolytic glaucoma or lens swelling and phacomorphic glaucoma.

Penetrating injury also presents the unique prospect of developing epithelial downgrowth. Here, epithelial cells grow through the wound and across the trabecular meshwork and other intraocular structures to obstruct aqueous outflow. This rare condition is exceedingly difficult to correct and should always be considered when the eye remains chronically irritated with pressure elevation following a prior penetrating injury. It is discussed in Chapter 28.

GLAUCOMA WITH RETAINED FOREIGN BODY

Retained foreign bodies are a relatively uncommon cause of late onset glaucoma following penetrating trauma. In one series of 153 patients with posterior segment intraocular foreign bodies, there was a 5% incidence of glaucoma, excluding patients with lens-induced mechanisms.⁵⁸

Siderosis

Metallic intraocular foreign bodies may release iron that is toxic to the retina and trabecular meshwork. Accumulation of iron ions in intraocular epithelial structures can lead to anterior subcapsular cataract, glaucoma, uveitis, and retinal degeneration.

Eyes with siderosis demonstrate heterochromia, mydriasis, and elevated IOP. Slit-lamp examination reveals a rust-brown color of the deep cornea, trabecular meshwork, and anterior subcapsular regions of the lens.⁵⁹ An electroretinogram can significantly aid the diagnosis of siderosis and may reveal changes before the visual acuity is affected.

Once the diagnosis is suspected, the clinician should inspect the eye for signs of penetration. This includes slit-lamp examination for evidence of a sealed corneal perforation or a hole or transillumination defect in the iris, and for direct visualization of the foreign body (Table 24–4). Ultrasonography and computed tomography can also help to confirm the clinical suspicion.

Chalcosis

Oxidization of foreign bodies in the eye containing more than 85 percent copper can damage the cornea, lens, uvea, and retina.⁶⁰ The retinal damage may cause visual field defects that mimic glaucoma.⁶¹ However, IOP elevation is apparently less frequently associated with chalcosis. Prompt removal of the foreign body, if possible, is important to avoid ocular pathology.

TABLE 24–4 SIGNS OF PAST TRAUMA OR PENETRATING FOREIGN BODIES

<i>Signs of Past Trauma</i>	<i>Signs of Penetrating Foreign Body</i>
Lid or facial scars	Sealed corneal perforation
Excessively deep anterior chamber	Conjunctival chemosis
Anterior chamber asymmetry	Hypotony
Pupillary sphincter tears	Iris color changed
Iridoschisis	Hole or transillumination defect in iris
Iridodonesis or phacodonesis	Visualization of foreign body
Vossius' ring	Lens capsular rupture or cataract

CHEMICAL BURNS

Ocular chemical injuries can lead to either hypotony or elevated IOP, depending on the type of chemical and the duration of time from the initial injury. Alkalies rapidly penetrate the cornea.⁶² Increased concentration of these chemicals in the anterior chamber leads to more extensive damage to intraocular tissues, including the trabecular meshwork. In contrast, acidic chemicals will coagulate corneal epithelial and stromal proteins, forming a natural barrier to deep penetration.

Shortly after the injury, the IOP may be elevated due to inflammation, anterior segment shrinkage, or increased uveal blood flow.⁶³ Severe inflammation or damage to the ciliary body typically leads to a decrease in aqueous production and hypotony.

In following weeks or months, ongoing inflammation or scar formation may cause pressure elevation by several mechanisms, including direct trabecular meshwork damage from the initial chemical injury, and angle-closure glaucoma from peripheral anterior synechiae formation or from posterior synechiae and pupillary block.

The diagnosis and monitoring of elevated IOP following severe chemical injuries is often challenging. In general, corneal scarring reduces the accuracy of Goldmann applanation and Schiøtz tonometry, and many clinicians prefer the Tono-pen or a pneumotonometer in this situation. Evaluation of the optic disc appearance and visual fields is frequently hampered by poor corneal clarity and reduced acuity.

PITFALL... Corneal scarring following a chemical burn can reduce the accuracy of Goldmann applanation tonometry, and many clinicians prefer the Tono-pen or a pneumotonometer in this situation.

Management of chemical injuries always begins with immediate, copious irrigation of the involved eye. If

glaucoma develops, systemic glaucoma therapy may be necessary because topical medications can impair re-epithelialization of the ocular surface. In addition, epinephrine and prostaglandin analogs can aggravate inflammation, and pilocarpine causes shallowing of the chamber and miosis, which can encourage the formation of anterior and posterior synechiae. Corticosteroids are controversial in this situation. Although they minimize anterior segment inflammation, they may also increase the potential for corneal melt. Surgical glaucoma management is also challenging because filtering procedures are unlikely to succeed in the face of extensive conjunctival scarring. Aqueous shunts may prove effective, however.

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LENS-INDUCED GLAUCOMA

F. Jane Durcan, M.D.

Lens pathology can lead to either open- or closed-angle glaucoma, and often, a combination of both. The open-angle forms of glaucoma generally result from blockage of the aqueous drainage system with lens material and inflammatory debris. These include: phacolytic glaucoma, lens particle glaucoma, and phacoanaphylactic glaucoma. In the angle-closure group, the lens causes direct mechanical closure of the angle. This occurs with an intumescent lens in phacomorphic glaucoma or with a subluxated or dislocated lens in ectopia lentis. Any of the open-angle conditions can lead to angle-closure glaucoma if they induce sufficient inflammation to cause the formation of peripheral anterior synechiae or posterior synechiae.

PHACOLYTIC GLAUCOMA

Phacolytic glaucoma refers to the acute development of open-angle glaucoma resulting from leakage of lenticular proteins through the intact capsule of a mature or hypermature cataract. The rise in intraocular pressure probably results from obstruction of the trabecular meshwork by high-molecular-weight proteins and macrophages. The clinical picture is distinguished from other acute glaucomas by the presence of a mature or hypermature lens and the presence of large, translucent cells in the anterior chamber. Removal of the cataractous lens usually allows rapid control of the intraocular pressure.

BACKGROUND

Gifford first described the clinical presentation of phacolytic glaucoma in 1900.¹ In 1943, Zeeman associated the glaucoma with a macrophage response to lens material leaking from a hypermature cataract,² and Irvine and Irvine later postulated that increased intraocular pressure resulted from blockage of the trabecular meshwork by these macrophages.³ Flocks first used the term *phacolytic*

glaucoma in 1955,⁴ but the role of high-molecular-weight lens proteins in obstructing aqueous humor outflow was not defined until the late 1970s.^{11,12} Phacolytic glaucoma is now relatively rare in developed countries due to improvements in cataract surgery techniques and because cataracts are generally removed long before they reach maturity. However, it continues to be a problem in countries with more limited access to care.^{5,6}

PATHOPHYSIOLOGY

Phacolytic glaucoma probably results from obstruction of the trabecular meshwork by macrophages and by high-molecular-weight lens proteins, which increase in the lens with age and cataract formation.⁷ In mature and hypermature cataracts, these proteins, which are also chemotactic for macrophages,⁸ can leak into the anterior and posterior chambers through microscopic defects in the lens capsule. This is supported by pathologic studies of eyes with phacolytic glaucoma demonstrating eosinophilic, protein-like material in the trabecular meshwork,⁹ as well as macrophages containing phagocytosed lens particles (Fig. 25–1).¹⁰ Epstein et al identified high levels of high-molecular-weight proteins in patients with mature or hypermature cataracts undergoing cataract surgery for presumed phacolytic glaucoma.¹¹ They also showed that such proteins can decrease outflow facility in cadaver eyes by blocking the trabecular meshwork.¹² Thus, although the macrophages probably phagocytose and remove lens proteins, their presence in the trabecular meshwork may not be necessary to cause the elevated IOP.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The symptoms of phacolytic glaucoma resemble those of any acute glaucoma (Table 25–1). Vision loss associated with the onset of phacolytic glaucoma is usually severe

TABLE 25-1 DIAGNOSIS OF PHACOLYTIC GLAUCOMA

Symptoms	Decreased vision Pain Progressive visual loss prior to attack
Signs	Conjunctival injection Mature (hypermature) cataract Dense flare and large cells in anterior chamber with white material Vitreous opacities Macrophages in aqueous humor

and generally results from corneal edema and inflammation. Prior to the attack, most patients undergo a slow progressive visual loss over months to years, consistent with a developing cataract.

Findings usually include acute and severe elevation of intraocular pressure, mature or hypermature cataract, dense flare, and large cells in the aqueous. Keratic precipitates are uncommon and usually limited to the peripheral corneal endothelium. Anterior segment examination, which may require topical glycerin to clear corneal epithelial edema, can reveal white patches on the anterior capsule, and clumps of white material floating in the anterior chamber, occasionally forming a pseudohypopyon. Histologic studies suggest that this white material may consist of macrophages, cholesterol-like crystals, and liquified cortical material.^{4,13} The angle is usually open, although Smith and Zimmerman found angle recession in 25% of cases.¹⁴ Posterior segment findings include opacities in the vitreous¹⁵ and retinal perivasculitis.¹⁶

PEARL... Primary features of phacolytic glaucoma include: mature or hypermature cataract, an intact capsule, marked flare, and large aqueous cells.

Additional studies include specular microscopy to improve the identification of macrophages, which appear as rounded, swollen cells about three times the size of an erythrocyte. A diagnostic paracentesis with concentration of the aqueous sample on a millipore filter and phase contrast microscopy may also help detect macrophages in cases where the need for cataract extraction is not immediately apparent.¹⁷

The differential diagnosis of phacolytic glaucoma appears in Table 25-2. Gonioscopy should clearly identify acute angle-closure and phacomorphic glaucoma because these both have narrow or closed angles. Eyes with lens particle glaucoma should have a history of trauma or prior lens surgery and evidence of free floating lens material, more fully discussed in the following text. Normal iris vessels may be engorged in phacolytic glaucoma. However, these are distinct from the finer, matted vessels seen at the pupillary margin and in the angle in neovascular glaucoma.

Examination of the cellular reaction in the anterior chamber may also help differentiate phacolytic glaucoma from other uveitis syndromes, primarily since macrophages are larger and more translucent than the smaller leukocytes of idiopathic uveitis or the khaki-colored cells seen in some posttraumatic glaucomas. Iridescent particles of cholesterol may also appear in phacolytic glaucoma. A history of recent systemic infection, particularly in an immunocompromised patient, should raise suspicions of endogenous endophthalmitis. Whereas recent trauma would implicate a traumatic uveitis and glaucoma, the presence of uveitis may make angle recession glaucoma less likely.

MANAGEMENT

Definitive management requires removal of the cataract. To avoid operating on an inflamed eye with high pressure, initial management should concentrate on reducing inflammation with intense topical and, occasionally, oral,

TABLE 25-2 DIFFERENTIAL DIAGNOSIS OF PHACOLYTIC GLAUCOMA

Condition	Differentiating Features
Acute angle-closure glaucoma in a cataractous eye	Narrow angle on gonioscopy
Phacomorphic glaucoma	Narrow angle on gonioscopy
Uveitic glaucoma	White blood cells are smaller than macrophages
Neovascular glaucoma	Abnormal vessels in pupillary margin and angle
Endogenous endophthalmitis	A history of infection in an immunocompromised host Positive culture
Traumatic angle recession glaucoma and cataract	History of trauma Angle recession on gonioscopy Absence of uveitis
Trauma-induced uveitic glaucoma and cataract	History of trauma White blood cells smaller than macrophages
Lens particle glaucoma	Break in capsule Free-floating lens material

corticosteroids. Aqueous suppressants, such as topical beta-blockers, alpha agonists, and either topical or oral carbonic anhydrase inhibitors are usually indicated to control IOP while avoiding miotics and prostaglandin analogs. In severe cases, oral or intravenous hyperosmotic agents can provide temporary pressure control.

Persistence of severe inflammation and intraocular pressure elevation forces prompt removal of the lens. Although intracapsular cataract extraction was previously

advocated, extracapsular surgery with posterior chamber intraocular lens implantation can lead to good results without persistent inflammation (Fig. 25-1C,D).¹⁸

Current instrumentation and chopping techniques now permit the surgeon to break even hard lenses into small pieces that can be removed either in chunks through a small incision or, in some cases completely, by phacoemulsification. This hinges on continuous curvilinear capsulorhexis, which may be performed with an endoilluminator to help

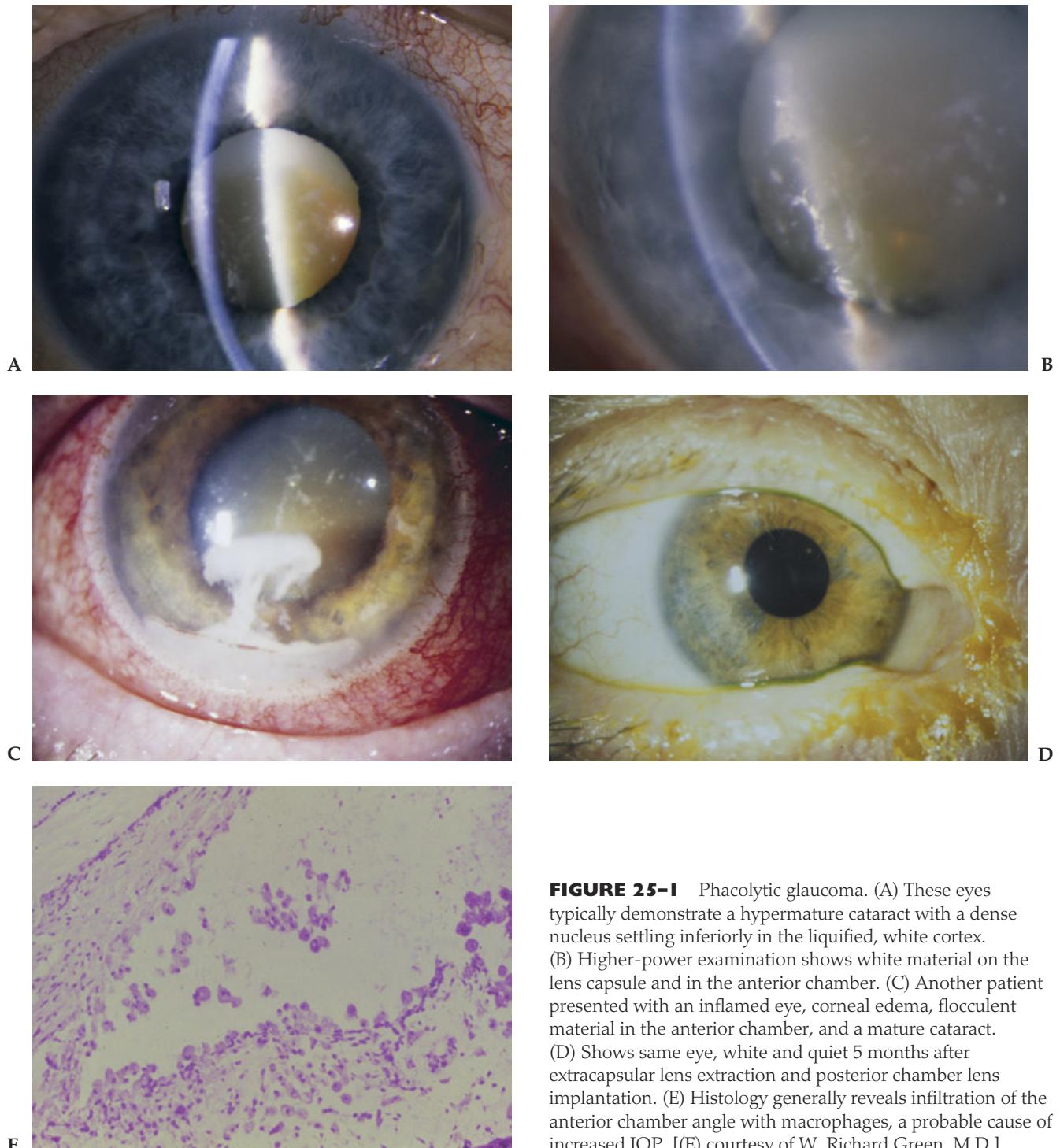


FIGURE 25-1 Phacolytic glaucoma. (A) These eyes typically demonstrate a hypermature cataract with a dense nucleus settling inferiorly in the liquified, white cortex. (B) Higher-power examination shows white material on the lens capsule and in the anterior chamber. (C) Another patient presented with an inflamed eye, corneal edema, flocculent material in the anterior chamber, and a mature cataract. (D) Shows same eye, white and quiet 5 months after extracapsular lens extraction and posterior chamber lens implantation. (E) Histology generally reveals infiltration of the anterior chamber angle with macrophages, a probable cause of increased IOP. [(E) courtesy of W. Richard Green, M.D.]

reveal the capsule edge.¹⁹ A scissors capsulotomy,²⁰ or a two-stage technique with an initial small capsulorhexis and endophacoemulsification followed by enlargement of the capsulorhexis, is also effective in this situation.²¹ Perhaps most encouraging are recent reports of staining of the anterior capsule by indocyanine green²² and fluorescein blue for improved visibility of the capsulorhexis.²³

Regardless of surgical technique, the surgeon must decompress the eye slowly when entering it, while using a dispersive viscoelastic to improve visualization. The opaque, often liquid cortex is then removed by irrigation after capsulotomy, or by needle aspiration through a small capsular incision.²⁴ Postoperatively, fibrinous anterior chamber reaction usually resolves following a few days of copious topical steroids. Prompt treatment usually leads to a good prognosis for both vision and intraocular pressure control.

CONTROVERSY

Although intracapsular cataract extraction has long been advocated for phacolytic glaucoma, improvements in phacoemulsification techniques now make this a viable option.

LENS PARTICLE GLAUCOMA

Extracapsular cataract extraction, traumatic perforation of the lens capsule, and neodymium:yttrium-aluminum-garnet (Nd:YAG) capsulotomy can all liberate lens material into the aqueous humor. This material can obstruct aqueous outflow and elevate intraocular pressure, producing lens particle glaucoma. These patients usually present following ocular surgery or trauma with elevated intraocular pressure and uveitis, often with visible cortical material in the anterior chamber. Treatment includes corticosteroids and glaucoma medications, although many eyes require surgical removal of the lenticular material.

BACKGROUND

Despite the increasing popularity of extracapsular cataract techniques, lens particle glaucoma remains relatively uncommon. This may be due to improved methods and instrumentation for removing lens cortex. Another factor influencing development of this complication is a poor facility of aqueous outflow.²⁵ Patients with open-angle glaucoma tolerate retained cortical material more poorly than patients with a healthy outflow mechanism.

PATHOPHYSIOLOGY

Histologic studies have demonstrated both free lens material, which can obstruct aqueous outflow channels,¹² and monocytes, which the lens proteins attract,⁸ within

the trabecular meshwork.⁹ One specimen, probably a combination of phacolytic and lens particle glaucoma, included phacolytic cells (macrophages with degenerated lens material), melanin-laden macrophages, erythrocytes, ghost cells, lymphocytes, and macrophages containing erythrocytes, leukocytes, and degenerated macrophages.¹⁰ The trabecular meshwork specimen contained phacolytic cells, cell debris, and free-floating lens material.

In most cases, the elevated pressure probably results from obstruction by lens material and cellular debris. In contrast, lens particle glaucoma following Nd:YAG capsulotomy is thought to arise from trabecular meshwork blockage by small lens fragments and soluble proteins, shock wave damage, and, possibly, vitreous molecules.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Patients present with inflammation and elevated intraocular pressure, usually days to weeks following extracapsular cataract extraction, traumatic lens rupture, or Nd:YAG capsulotomy (Table 25–3). They may have discomfort, redness, and decreased vision.

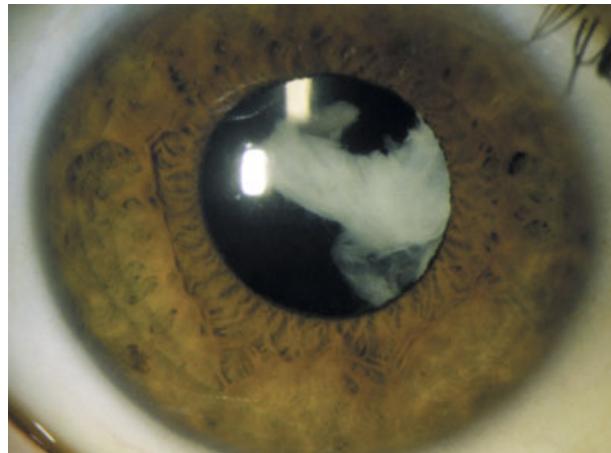
Signs include cataract remnants within the posterior chamber, fragments of white cortical material floating in the aqueous, and lens debris on the endothelium (Fig. 25–2A,B). Although often obscured by corneal edema, flare and circulating leukocytes and macrophages are usually present. Although a hypopyon is possible, lens material may settle out in the inferior angle and be difficult to see without gonioscopy. A diagnostic anterior chamber tap can retrieve both white blood cells and lens material.

The differential diagnosis of lens particle glaucoma appears in Table 25–4. Because of its rapidly progressive, potentially devastating course, infectious endophthalmitis must be ruled out quickly. Lens particle glaucoma is generally more subacute and the presence of visible lens material is key to the correct diagnosis. A paracentesis can help diagnose either condition.

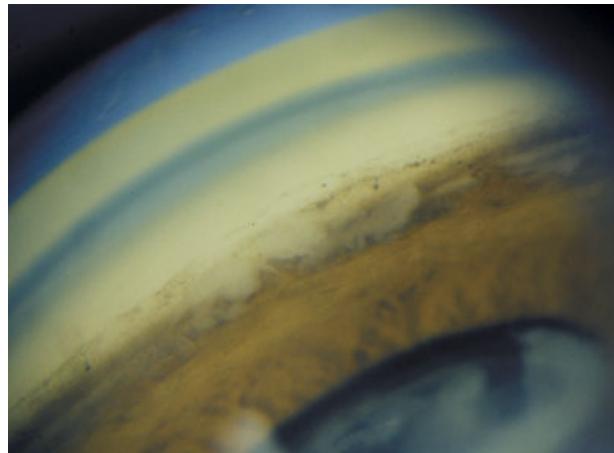
Phacoanaphylactic glaucoma is primarily a histologic diagnosis, often made only after all the lens material, including the capsule, is removed and, occasionally, after enucleation. A history of prior uveitis, or of signs and symptoms consistent with systemic disease associated with uveitis, may help differentiate other uveitic glaucomas from lens particle glaucoma. Any case of severe uveitis and glaucoma following trauma should be examined carefully

TABLE 25–3 DIAGNOSIS OF LENS PARTICLE GLAUCOMA

Symptoms	Onset following ocular surgery or trauma Decreased vision Pain
Signs	Conjunctival injection Cortical material and lens debris in aqueous Hypopyon (may be obscured) Circulating leukocytes and macrophages



A



B

FIGURE 25-2 Lens particle glaucoma following cataract extraction. (A) Retained superior cortex has slipped into the pupil, with cortical material in the inferior angle, (B) visible only by gonioscopy.

for evidence of lens capsule rupture and lens particle glaucoma, remembering that severe corneal edema may obscure free lens material. Finally, uveitis following Nd:YAG capsulotomy can occasionally develop from an indolent *Propionibacterium acnes* infection.²⁶

MANAGEMENT

Medical management involves directly treating the IOP and controlling inflammation. This requires aqueous suppressants, such as beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and occasionally, hyperosmotic agents²⁷ in addition to topical and, if necessary, oral corticosteroids. Cycloplegics often improve comfort and can prevent the formation of posterior synechiae. Miotics and prostaglandin analogs are contraindicated because they may exacerbate the inflammation. If these measures fail, surgical removal of all lens debris is indicated to prevent their entrapment in inflammatory membranes, permanent scarring, and irreversible glaucoma.

TABLE 25-4 DIFFERENTIAL DIAGNOSIS OF LENS PARTICLE GLAUCOMA

Condition	Differentiating Features
Acute infectious endophthalmitis	Rapidly progressive Positive gram stain and culture
Phacoanaphylactic glaucoma	Inexorable course Zonal inflammation on pathology
Uveitic glaucoma	Prior history of uveitis Systemic signs and symptoms of uveitic syndromes
Traumatic uveitis and glaucoma	No visible lens rupture or free-floating lens material
Phacolytic glaucoma	No history of trauma or prior lens surgery
<i>P. acnes</i> infection	Positive culture

PHACOANAPHYLACTIC GLAUCOMA

Phacoanaphylaxis is a rare, granulomatous inflammation directed against sequestered lens material. This usually follows extracapsular cataract extraction or phacoemulsification, or spontaneous, traumatic, or surgical lens rupture.^{28,29} The uveitis is chronic and unrelenting and may cause glaucoma through blockage of the trabecular meshwork by inflammatory debris, pupillary block from posterior synechiae, or angle closure from peripheral anterior synechiae. This is almost always a retrospective, histopathologic diagnosis, and treatment requires removal of the inciting lens material.

BACKGROUND

Phacoanaphylactic endophthalmitis was first recognized in 1919, and Verhoeff and Lemoine defined the condition in 1922.²⁸ However, the first case with a favorable outcome did not appear until 1965,²⁹ when Riise reported a magical clearing of the uveitis after removal of the posterior capsule. Despite the resurgence of extracapsular cataract extraction, the rate of phacoanaphylactic endophthalmitis has remained low.

PATHOPHYSIOLOGY

Histologic examination reveals a zonal, granulomatous inflammatory reaction, with polymorphonuclear leukocytes surrounding a nidus of damaged or retained lens material (Fig. 25-3).³⁰⁻³² This is encircled by successive zones of granulomatous inflammation containing multinucleated giant cells and, finally, a nonspecific layer of mononuclear cells, often with eosinophils, plasma cells, and histiocytes. Although some investigators theorize that this reaction represents an immune rejection of sequestered, foreign lens material, others have suggested it is an immune complex disease that develops in response

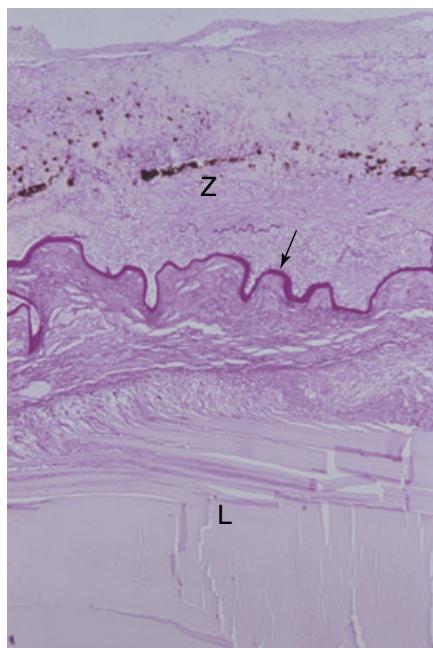


FIGURE 25-3 Phacoanaphylactic glaucoma. Low-power photomicrograph of a periodic acid-Schiff stained specimen, showing disrupted capsule (arrow) and lens material (L) surrounded by zonal inflammation (Z). (Courtesy of Nick Mamalis, M.D.)

to the loss of the normal tolerance to lens proteins.^{33,34} Although firmly entrenched in the literature, the term *phacoanaphylaxis* is misleading because this does not appear to be an IgE mediated phenomenon.

Glaucoma with phacoanaphylactic endophthalmitis may occur with an open angle, angle closure, or a combination of both. Open-angle glaucoma primarily results from blockage of the trabecular meshwork with free lens particles and proteins, lens material, and inflammatory cells. Other potential open-angle mechanisms include direct inflammation of the trabecular meshwork and steroid-induced elevation in intraocular pressure. Angle-closure glaucoma can result from the development of peripheral anterior synechiae and pupillary block from extensive posterior synechiae.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The reported incidence of all forms of persistent, post-operative uveitis, from which phacoanaphylactic endophthalmitis must be differentiated, is between 1³⁵ and 2%.³⁶ Although phacoanaphylactic endophthalmitis typically begins within 1 day to 2 weeks, onset may range from only hours to several months after the inciting surgery or trauma. Loss of vision, pain, and anterior chamber reaction from uveitis can vary from mild to severe (Table 25-5).

Biomicroscopic examination reveals a prominent anterior chamber cellular response. Unlike phacolytic

TABLE 25-5 DIAGNOSIS OF PHACOANAPHYLACTIC GLAUCOMA

Symptoms	Onset typically days to weeks following ocular surgery or trauma Decreased vision Pain
Signs	Anterior chamber cells and flare Keratic precipitates Hypopyon Anterior and posterior synechiae Vitreous opacities and membranes Macular edema

glaucoma, keratic precipitates are common here, and peripheral anterior synechiae and posterior synechiae may form. A hypopyon may recur as the inflammation waxes and wanes in response to treatment. Definitive diagnosis relies on the histopathologic demonstration of a typical, zonal granulomatous response.

Table 25-6 lists the differential diagnosis of phacoanaphylactic glaucoma. Gram stain and culture of a diagnostic anterior chamber or vitreous tap can help identify infectious endophthalmitis, whereas the presence of lens material would support either phacoanaphylactic glaucoma or lens particle glaucoma. These forms of glaucoma can be differentiated by histologic examination of sequestered lens material. Recent manufacturing improvements have markedly improved ocular tolerance to intraocular lenses. However, lenses in the ciliary sulcus or anterior chamber can still irritate uveal tissue and promote chronic inflammation; this mechanism must be considered whenever the intraocular lens has not been placed in the capsular bag.

MANAGEMENT

Initial management is directed toward controlling intraocular inflammation. Unfortunately, although topical, subconjunctival, and even systemic corticosteroids³⁷ may produce an initial improvement in the uveitis, this is often followed by a worsening course. The medical treatment of intraocular pressure consists primarily of aqueous suppressants and avoiding miotics and latanoprost. Steroid response of the intraocular pressure in susceptible patients may further complicate glaucoma treatment.

Removing the lens remnants and the intimately associated intraocular lens constitutes definitive treatment for phacoanaphylactic endophthalmitis. The entire lens capsule and lens remnants can be manually removed through the anterior segment with the aid of alpha-chymotrypsin, whereas a mechanical pars plana vitrectomy technique may be preferred in some patients. Eyes with pupillary block may require laser or surgical peripheral iridectomy to reverse glaucoma and prevent

TABLE 25-6 DIFFERENTIAL DIAGNOSIS OF PHACOANAPHYLACTIC GLAUCOMA

Condition	Differentiating Features
Infectious endophthalmitis	Positive gram stain and culture
Lens particle glaucoma	No zonal inflammatory response to sequestered lens material on pathology
Intraocular lens complication	Intraocular lens poorly placed in uveal tissue Iris transillumination defects
Intraocular foreign body	Visualization of intraocular foreign body Ultrasound Neuroimaging
Sympathetic ophthalmia	History of prior surgery or trauma in fellow eye Dalen-Fuchs nodules
Uveitic glaucoma	No history of ocular surgery or trauma. No evidence of lens material

permanent angle closure. Treatment of glaucoma that persists even after complete control of the inflammation often includes either a trabeculectomy with antimetabolites, or valve implantation.

PHACOMORPHIC GLAUCOMA

Phacomorphic glaucoma results from angle closure caused by enlargement of the crystalline lens, anterior displacement of the peripheral iris, and angle closure (Fig. 25-4A,B). The diagnosis hinges on identifying angle closure by gonioscopy that persists despite peripheral iridotomy, in conjunction with a lens that is large relative to the size of the eye and often cataractous. Cataract extraction often cures this form of glaucoma.

BACKGROUND

Improved access to ophthalmologic care and modern cataract surgery techniques have both decreased the incidence of this form of glaucoma, although it may again increase as baby boomers age and life expectancy rises. However, it is still a problem in developing countries,^{5,6}

and even in industrialized nations with limited access to cataract surgery.³⁸ Hyperopes and the elderly are at higher risk for this condition.

PATHOPHYSIOLOGY

Phacomorphic glaucoma results from angle closure caused by anterior mechanical forces of the lens on the iris. Hyperopic eyes, with lenses that are already large relative to their axial lengths, have inherently narrower anterior chambers and are predisposed to this condition.

Further lens enlargement can result from several factors. These include age, during which the lens increases in thickness and develops a greater anterior curvature, and lens trauma, which encourages lens intumescence. Less common causes of lens swelling include diabetes and lens intumescence from an idiosyncratic reaction to systemic medications, such as some diuretics.³⁹ In persistent hyperplastic primary vitreous (PHPV), rupture of the posterior lens capsule can produce rapid cataract formation, whereas contraction of the fibrovascular membrane can force the lens–iris diaphragm forward and produce anterior chamber shallowing.⁴⁰ Retinopathy of prematurity

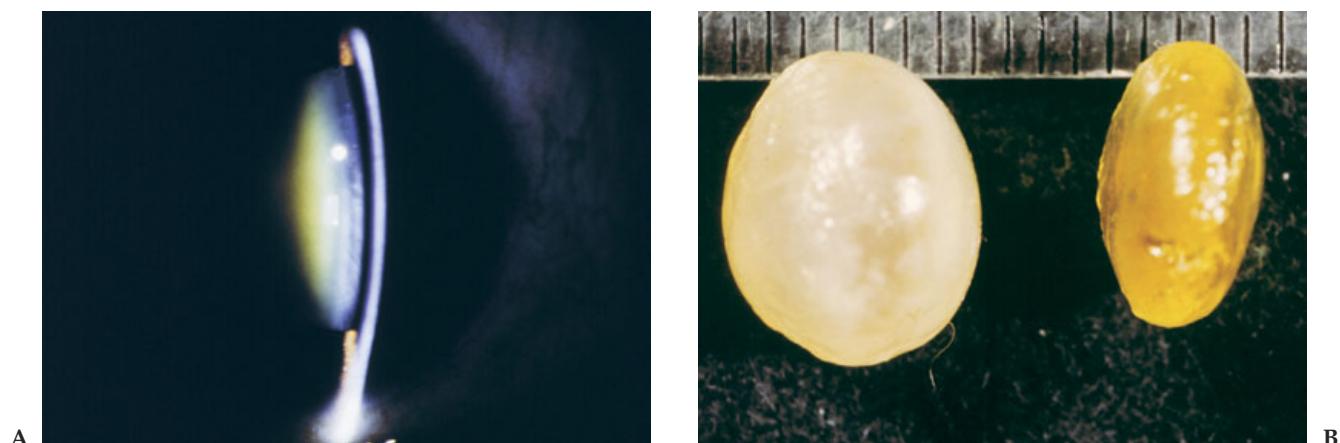


FIGURE 25-4 Phacomorphic glaucoma. (A) The anterior chamber is typically shallow centrally and peripherally, presumably due to forward pressure on the iris by a swollen, cataractous lens. (B) Pathologic specimens, comparing relative anteroposterior diameters of an intumescent lens and a normal lens. [(B) courtesy of W. Richard Green, M.D.]

can also cause forward displacement of the lens–iris diaphragm.⁴¹ Other causative factors of phacomorphic glaucoma, such as trauma and pseudoexfoliation,⁴² can affect zonular support and allow anterior displacement of the lens.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Symptoms of chronic phacomorphic glaucoma are generally limited to decreasing vision secondary to cataract formation and a myopic shift. However, some patients may seek medical attention because of superimposed pupillary block, with acute symptoms of pain, nausea, and rapid visual loss. Although gonioscopy reveals a narrow angle in both conditions, gonioscopy following peripheral iridotomy provides the ultimate test. Persistent angle closure despite a patent iridotomy strongly supports anterior displacement of the iris by the lens, and phacomorphic glaucoma (Table 25–7).

PEARL... A peripheral iridotomy helps distinguish phacomorphic glaucoma in an eye with a cataract from pupillary block glaucoma.

MANAGEMENT

Treatment of patients with an acute rise in intraocular pressure must first address any possible component of pupillary block. This includes aqueous suppressants and hyperosmotics. Miotics must be used cautiously. Although they may reduce peripheral angle crowding, they can also shift the lens–iris diaphragm anteriorly and exacerbate the angle closure. Depressing the central cornea with a Zeiss four-mirror lens or with digital massage may also help break a pupillary block attack.

A laser iridotomy can benefit the surgical treatment of phacomorphic glaucoma in several ways. In eyes with at least some acute angle closure secondary to pupillary block it can reduce intraocular pressure and inflammation before cataract extraction. Iridotomy also increases the safety of preoperative mydriasis and aids the assessment of the extent of peripheral anterior synechiae and the

TABLE 25–7 DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PHACOMORPHIC GLAUCOMA

Condition	Features
Phacomorphic glaucoma	Subacute, gradual decreased vision Disparity in anterior chamber depth, cataract formation, and angle configuration between eyes Angle closure persists despite patent iridotomy
Pupillary block glaucoma	Acute pain, nausea, and decreased vision Usually relieved by laser peripheral iridotomy

need for a trabeculectomy prior to surgery.⁴² In refractory cases, laser iridoplasty may help pull the iris away from the angle, although this effect is usually only transient.⁴³

Removal of the lens usually cures phacomorphic glaucoma, and is clearly indicated in cases with a visually significant cataract. However, clear lens extraction in this situation is more controversial. Eyes with significant peripheral anterior synechiae may require a trabeculectomy or combined procedure for long-term pressure control. Careful gonioscopy helps determine the correct operative plan.

ECTOPIA LENTIS

Ectopia lentis refers to either subluxation or dislocation of the natural lens from its normal position behind the pupil. With either mechanism, the mobile lens mechanically obstructs aqueous humor outflow, resulting in angle-closure glaucoma. The main diagnostic dilemma presented by ectopia lentis lies in differentiating between the many systemic syndromes associated with this condition and a traumatic etiology. Although management is usually conservative, some eyes require surgical intervention, either laser peripheral iridotomy or lens extraction, to control the pressure.

BACKGROUND

Lens subluxation generally results from loosening, disruption, or breakage of some, but not all, zonules. Although no longer centered, the lens remains behind the iris. With dislocation, all the zonules are broken. The lens may remain centered behind the iris, drop into the vitreous, or move into the anterior chamber.⁵⁷

Although Berryat described a case of bilateral anterior chamber lens displacement in 1749, Stellwag first used the term *ectopia lentis* in 1856. In 1846, Sichel noted the difference between spontaneous and traumatic dislocation and, 3 years later, Arlt proposed that congenital factors could contribute to childhood dislocations.⁴⁴ We now recognize that ectopia lentis can be traumatic, secondary, or congenital. Trauma can be accidental or surgical. Secondary dislocations are acquired and may be associated with other ocular diseases such as buphthalmos, pseudoexfoliation, high myopia, intraocular tumor, mature or hypermature cataract, syphilis, and uveitis.⁵⁷ Congenital ectopia lentis is associated with numerous systemic syndromes that will be discussed in the following section on diagnosis and differential diagnosis.

PATHOPHYSIOLOGY

Abnormalities of lens zonules underlie all forms of ectopia lentis. Trauma, the most common cause of zonular pathology, can both rupture zonules and cause ciliary spasm (Fig. 25–5A). This encourages forward movement of the lens, angle narrowing, and pupillary block. In congenital syndromes, such as Marfan's syndrome, homocys-

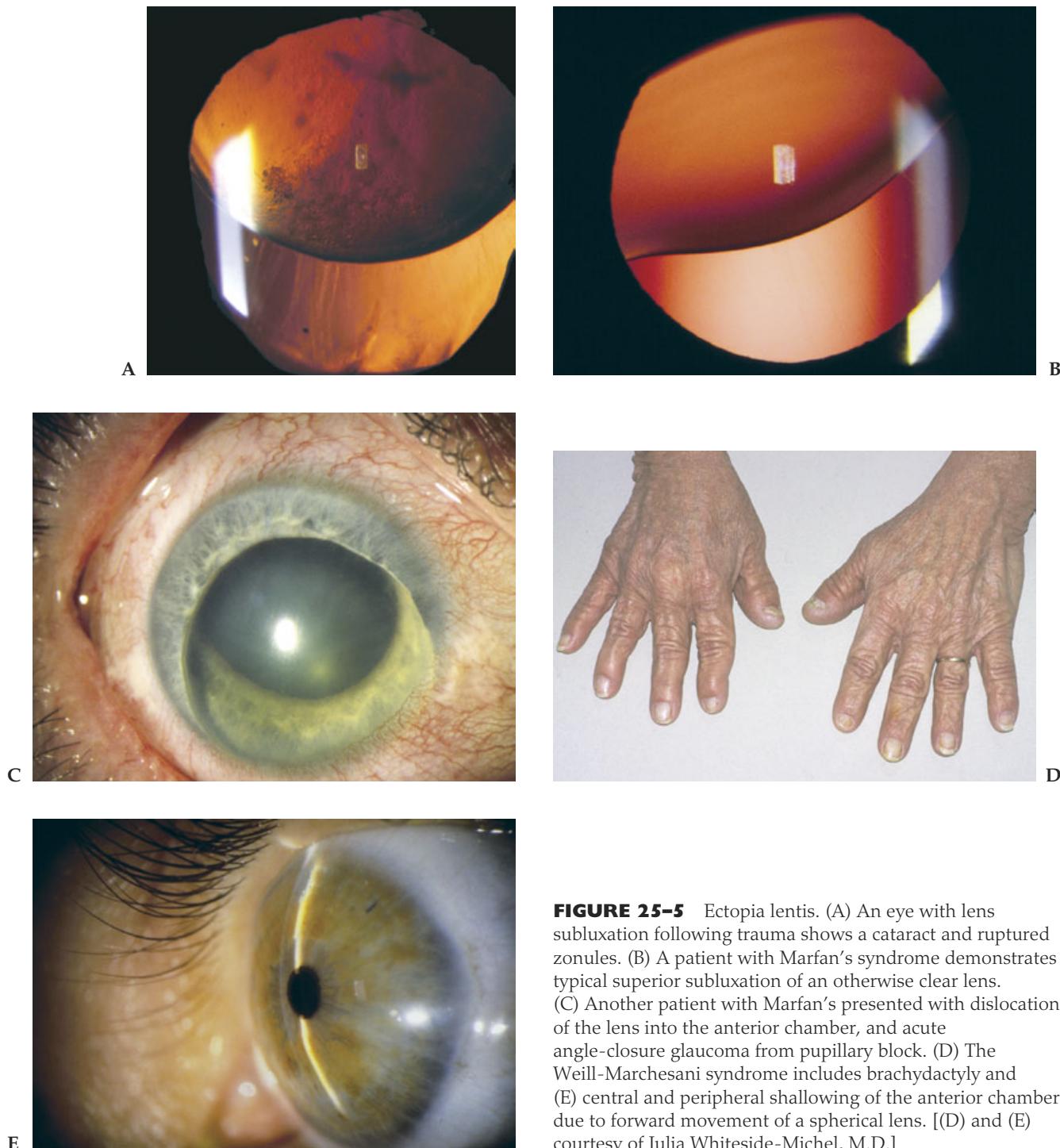


FIGURE 25-5 Ectopia lentis. (A) An eye with lens subluxation following trauma shows a cataract and ruptured zonules. (B) A patient with Marfan's syndrome demonstrates typical superior subluxation of an otherwise clear lens. (C) Another patient with Marfan's presented with dislocation of the lens into the anterior chamber, and acute angle-closure glaucoma from pupillary block. (D) The Weill-Marchesani syndrome includes brachydactyly and (E) central and peripheral shallowing of the anterior chamber due to forward movement of a spherical lens. [(D) and (E) courtesy of Julia Whiteside-Michel, M.D.]

tinuria, or Ehlers-Danlos syndrome, abnormal zonule formation and weakness produce deficient lens support.

Whatever the cause, glaucoma usually results from pupillary block by the abnormal lens position and, less commonly, from pupillary obstruction by the lens and the vitreous, or the vitreous alone. In some cases, the lens dislocates completely into the anterior chamber and directly obstructs aqueous outflow. Repeated attacks of acute angle closure from pupillary block may lead to peripheral anterior

synechiae, along with chronic open-angle glaucoma due to long-term damage to the trabecular outflow system.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Ectopia lentis most commonly presents with changing vision (Table 25-8). This results primarily from induced myopia due to the loosened zonules, which can produce spherophakia and anterior displacement of the lens.

TABLE 25-8 DIAGNOSIS OF ECTOPIA LENTIS

Symptoms	Changing vision due to induced myopia, astigmatism (lens tilting or rotation), variable refraction Monocular diplopia
Signs	Mild to complete displacement of the lens Phacodonesis and iridodonesis Abnormal zonules Variable angle abnormalities depending on lens position Vitreous prolapse

Loose zonules can also induce astigmatism by allowing tilting, decentration, or rotation of the lens. Other effects include variable refraction from lens movement, diminished accommodation, and monocular diplopia, if the lens edge moves within the pupillary margin. In young children, these visual abnormalities may produce amblyopia.

Clinical signs vary from mild displacement of the lens to complete dislocation into the vitreous or the anterior chamber. Associated findings include prominent iridodonesis and phacodonesis, disparity in anterior chamber depth between the two eyes, and, when visible, zonules that are stretched, thickened, absent, or ruptured. The vitreous can migrate into the anterior chamber, or pseudoexfoliation material may appear on the anterior surface of the lens, pupillary border, and lens zonules. Gonioscopic findings vary considerably, depending on the position of the lens and how it distorts the iris. Marked deepening of the anterior chamber indicates posterior lens dislocation, whereas pupillary block produces forward bowing of the iris.

Several congenital syndromes are associated with ectopia lentis, often with severe systemic complications (Table 25-9). Simple ectopia lentis, which does not have other ocular or systemic findings, has a variable, but usually autosomal, dominant inheritance, and onset <10 years of age.^{45,46} The lens displacement, usually superior and temporal, is often bilateral.⁴⁷

Ectopia lentis et pupillae affects the entire eye. In this rare, usually autosomal recessive condition, the pupil and the lens are both displaced. Other findings include cataract, retinal detachment, persistent pupillary membranes, iridohyaloid adhesions, prominent iris processes, and axial myopia.⁴⁸ This syndrome tends to occur in families with a history of consanguinity.

Marfan's syndrome is the most common syndrome associated with ectopia lentis (Fig. 25-5B,C). This connective tissue disorder has been associated with abnormal fibrillin production,^{49,50} a genetic abnormality located on the long arm of chromosome 15 (15q21.1)⁵¹ and an autosomal dominant inheritance with high penetrance. Fifty to 80% of Marfan's patients develop ectopia lentis, with bilateral, superior, and temporal displacement.⁵² Other ocular findings include high myopia, an enlarged globe, flattened

TABLE 25-9 CAUSES OF ECTOPIA LENTIS

Condition	Features
Trauma	History of trauma Usually unilateral Signs of trauma
Pseudoexfoliation	Pseudoexfoliation material on the anterior lens capsule Increased pigment in the angle
Simple ectopia lentis	Family history (usually autosomal dominant) Usually bilateral Lens usually displaced superotemporally No other ocular or systemic abnormalities
Ectopia lentis et pupillae	Family history (usually autosomal recessive) Usually bilateral Consanguinity Pupil and lens displaced in opposite directions
Marfan's syndrome	Autosomal dominant Bilateral Lens displaced superotemporally Arachnodactyly, hyperextensible joints Cardiovascular abnormalities
Homocystinuria	Autosomal recessive Lens displaced nasally or inferonasally Arachnodactyly Cardiovascular abnormalities, mental retardation Platelet abnormalities, thromboembolic events following general anesthesia Nitroprusside test
Weill-Marchesani syndrome	Microspherophakia Brachymorphia, brachydactyly, brachycephaly
Ehlers-Danlos syndrome	Thin sclera
Sulfite oxidase deficiency	Bilateral Muscular rigidity, mental retardation
Hyperlysinemia	Mental retardation and hypotonia

corneas, and iris transillumination defects. Although gonioscopy reveals numerous iris processes, also common are vascular anomalies and peripheral mounds of iris tissue,⁵³ lattice degeneration, retinal holes, and retinal detachment.⁵⁴ Systemic findings include several musculoskeletal abnormalities and degenerative changes in the walls of major vessels.^{52,55}

Homocystinuria, an autosomal recessive disease characterized by the accumulation of homocystine in the blood and urine, appears to result from a deficiency or abnormality in cystathione beta synthase. The excess homocystine blocks condensation and cross-linking of collagen,⁵⁶ resulting in a variety of structural defects. Lens subluxation, usually inferior or inferonasal, occurs in 80

to 90% of patients,⁵⁴ and myopia is common. These patients can develop arachnodactyly and cardiac and ocular abnormalities. Half have mental retardation, which may be progressive.⁵²

Most importantly, patients with homocystinuria are prone to platelet abnormalities and thromboembolic events following general anesthesia, such as pulmonary embolism and stroke. Because of this serious complication, homocystinuria must be differentiated from Marfan's syndrome, with which it shares many features. Treatment consists of a diet low in methionine and high in homocystine and supplemental pyridoxine, in addition to low-dose aspirin.⁵⁷

PEARL... Patients with homocystinuria are at risk for thromboembolic events, particularly following general anesthesia.

The Weill-Marchesani syndrome, which has variable inheritance,⁵⁸ includes microspherophakia and the systemic findings of brachymorphia, brachydactyly, and brachycephaly (Fig. 25-5D,E).^{59,60} Although the zonules are usually intact, the small, round lens can sublux into the pupillary space, producing pupillary block glaucoma, which may be encouraged by miotics. Although mydriatics can increase tension on the zonules and pull the lens back into position, resistant cases may require laser peripheral iridectomy to prevent pupillary block.

PITFALL... Use of miotics in Weill-Marchesani syndrome may worsen pupillary block.

Several other systemic disorders may be associated with ectopia lentis. Patients with Ehlers-Danlos syndrome have abnormal collagen synthesis⁶¹ and extremely thin sclera, which can complicate ocular surgery.⁶² Bilateral ectopia lentis, muscular rigidity, and mental retardation are the hallmarks of sulfite oxidase deficiency.⁶³ In contrast, patients with hyperlysinemia, which also presents with mental retardation, have hypotonia.^{64,57}

The differential diagnosis of ectopia lentis associated with glaucoma appears in Table 25-10. This includes all traumatic forms of glaucoma, such as angle recession, hemolytic, uveitic, lens particle, and ghost cell glaucoma and also pseudoexfoliation. They may be distinguished by the history, and clinical evidence of angle recession, bleeding, or inflammation.

MANAGEMENT

Pupillary block associated with ectopia lentis responds best to laser peripheral iridotomy, which can also be used prophylactically in eyes with subluxated lenses. Although mydriatics help pull the lens–iris diaphragm posteriorly,

TABLE 25-10 DIFFERENTIAL DIAGNOSIS OF ECTOPIA LENTIS-ASSOCIATED GLAUCOMA

Condition	Differentiating Features
Traumatic angle recession glaucoma	Angle recession on gonioscopy
Traumatic hemolytic glaucoma	Presence of blood Open angle
Traumatic uveitic glaucoma	Uveitis prominent
Lens particle glaucoma	Uveitis and free lens material
Ghost cell glaucoma	Khaki-colored cells
Pseudoexfoliation glaucoma	Pseudoexfoliation material on anterior lens capsule Increased pigment in open angle

this may allow the lens or vitreous to move into the anterior chamber when the lens is dislocated or severely subluxated. Although miotics may help reverse pupillary block, they should be used judiciously and in low doses because they can paradoxically shallow the anterior chamber and aggravate pupillary block.

If the lens completely dislocates into the anterior chamber, placing the patient in the supine position and administering mydriatics, aqueous suppressants, and hyperosmotic agents may help relocate it posteriorly. On the other hand, posterior dislocation into the vitreous can be treated conservatively. However, a posteriorly dislocated lens needs continued observation because it can still become cataractous, produce phacolytic glaucoma, and require removal.

Surgical removal of dislocated and subluxated lenses is fraught with difficulty. Vitreous loss may occur in as many as 85% of these cases.⁶⁵ Although intracapsular cataract extraction was once the preferred method, advances in extracapsular techniques may even allow phacoemulsification in some traumatic cases. Clinical trials have shown that the Morcher ring, a flexible, horseshoe-shaped filament that can be dialed into the capsular bag to increase capsular support, is beneficial in cases of traumatic and pseudoexfoliation cataract extraction with limited zonular pathology.⁶⁶ A pars plana lensectomy and vitrectomy may well be the procedure of choice in congenital syndromes with severely subluxated or dislocated lenses.

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OCULAR INFLAMMATION AND GLAUCOMA

John C. Morrison, M.D., and James T. Rosenbaum, M.D.

Ocular inflammation can affect intraocular pressure (IOP) by either directly or indirectly altering aqueous humor dynamics. Although acute anterior uveitis can induce hypotony, glaucoma results when the inflammation primarily inhibits aqueous humor outflow. Medical management often controls this form of glaucoma, but prolonged or repeated attacks can permanently obstruct aqueous outflow and produce chronic glaucoma, which may ultimately require surgery.

Inflammation of the iris and ciliary body is commonly nonspecific and often responds to intensive topical corticosteroids. However, several distinct uveitic entities are associated with increased IOP, some of which primarily affect the cornea, sclera, and posterior uvea. Accurate diagnosis of these conditions can lead to more specific, effective management of the inflammation and prevent irreversible glaucoma.

PATHOPHYSIOLOGY

Aside from infections, the etiology of most ocular inflammation is poorly understood but often appears to represent an immune response. Uveitis, which involves the anterior (iris and ciliary body) and posterior uvea (choroid), is the inflammation most frequently associated with glaucoma. Table 26–1 lists the differential diagnosis of uveitis using four broad categories: syndromes generally confined to the eye; systemic, immune-mediated diseases that may also involve the uvea; infections; and masquerade syndromes that mimic ocular inflammatory disease. Representative conditions from each of these categories can cause glaucoma and are discussed in the following text.

Pathologically, anterior uveitis involves breakdown of capillary endothelial cell tight junctions, allowing leukocytes to traverse the normally impervious blood ocular barrier and accumulate in the iris, ciliary body, and anterior and posterior chambers. This abnormal vascular

permeability also leads to increased tissue concentrations of protein, which most likely enters the anterior chamber at the base of the iris within the ciliary body band.¹

Paradoxically, acute anterior uveitis can produce ocular hypotony as well as glaucoma, depending on the phase of the disease and the relative impact on aqueous humor formation and outflow. Hypotony may result from either reduced aqueous humor formation due to loss of ciliary epithelial gap junctions and disruption of the blood aqueous barrier, or from enhanced uveoscleral outflow.

Glaucoma from ocular inflammation develops when the facility for aqueous humor outflow falls below the rate of aqueous production. This may occur either with a gonioscopically open angle or with variable amounts of angle closure (Table 26–2).

Acute inflammatory glaucoma with an open anterior chamber angle usually results from direct obstruction of aqueous outflow channels by platelets, white blood cells, and macrophages, whose aggregation is favored by increased aqueous humor protein and high concentrations within the meshwork (Fig. 26–1A). These entrapped inflammatory cells may also affect trabecular function by releasing chemical mediators, such as cytokines, prostaglandins, and proteolytic enzymes, which encourage local inflammation, or trabeculitis. Chronic, irreversible glaucoma with an open angle generally results when repeated or chronic inflammation either produces permanent, local meshwork destruction or exceeds the capacity of trabecular endothelial cells to phagocytose and remove debris.

Many mediators of inflammation, including cytokines, prostaglandins, leukotrienes, platelet activating factor, and nitric oxide, can also affect IOP. This is clearly illustrated by the use of a prostaglandin F₂ analog to lower IOP. Theoretically, different forms of inflammation can evoke different mediators, which may have characteristic effects on either aqueous production or outflow. This, along with the anatomic site of inflammation, may

TABLE 26-1 DIAGNOSTIC CATEGORIZATION OF UVEITIS

Syndromes Confined Primarily to the Eye	Rubella Mumps Human T-Cell Lymphotropic Virus Type I Cytomegalovirus
Acute multifocal placoid pigmentary epitheliopathy Birdshot choroidopathy Fuchs' heterochromic cyclitis Glaucomatocyclitic crisis Lens-induced uveitis Multifocal choroiditis Pars planitis Serpiginous choroiditis Sympathetic ophthalmia Trabeculitis Trauma	Bacterial or Spirochetal Tuberculosis Leprosy Propriionibacterium Syphilis Whipple's disease Leptospirosis Brucellosis Lyme disease Bartonella Atypical mycobacteria
Suspected Immune-Mediated Diseases (Systemic)	Parasitic (Protozoan or Helminthic) Toxoplasmosis Acanthameba Toxocariasis Onchocerciasis Pneumocystis carinii Cysticercosis
Ankylosing spondylitis Behçet's disease Inflammatory bowel disease (Crohn's disease and ulcerative colitis) Drug or hypersensitivity reaction Interstitial nephritis Juvenile rheumatoid arthritis Kawasaki's disease Multiple sclerosis Psoriatic arthritis Reactive arthritis Relapsing polychondritis Rheumatic fever Sarcoidosis Systemic lupus erythematosus Vasculitis Vogt-Koyanagi-Harada syndrome	Fungal Histoplasmosis Coccidioidomycosis Candidiasis Aspergillosis Sporotrichosis Blastomycosis Cryptococcosis
Infectious Causes	Masquerade Syndromes
Viral Human immunodeficiency virus-I Herpes simplex Herpes zoster Epstein-Barr	Ischemia Leukemia Lymphoma Pigmentary dispersion Retinal detachment (Schwartz-Matsuо syndrome) Retinitis pigmentosa Retinoblastoma

explain, for instance, why the anterior uveitis of ankylosing spondylitis consistently lowers IOP, whereas herpes simplex keratouveitis raises it.

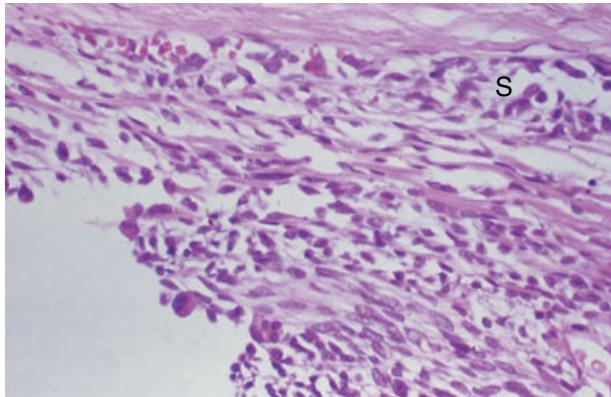
Angle-closure glaucoma from ocular inflammation probably results from a combination of peripheral iris swelling and local inflammation that leads to scarring and the formation of peripheral anterior synechiae, or adhesions, in the chamber angle (Fig. 26-1B). Although initially scattered, gradual spreading and coalescence of these adhesions, along with contraction of associ-

ated fibrovascular membranes, eventually obliterates the angle.

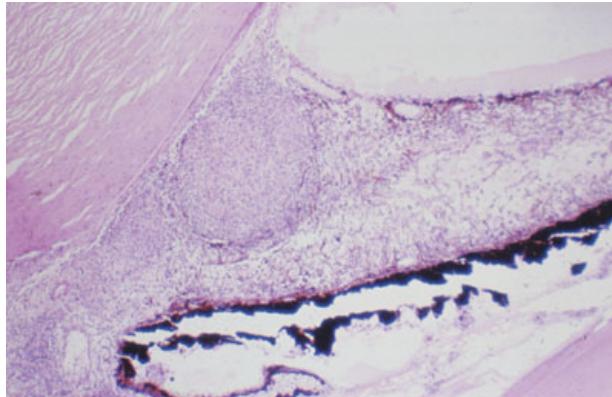
An acute and potentially reversible form of angle-closure glaucoma results from posterior synechiae, or iridolenticular adhesions that begin as fibrinous contacts and later evolve into permanent, fibrous bonds. Complete encirclement of the pupil with posterior synechiae (occluded pupil), often with a membrane over the lens (secluded pupil), blocks aqueous humor flow through the pupil into the anterior chamber (pupillary block). Subsequent

TABLE 26-2 MECHANISMS OF GLAUCOMA WITH OCULAR INFLAMMATION

<i>Open Angle</i>	<i>Closed Angle</i>
Obstruction of trabecular meshwork by microscopic inflammatory debris	Peripheral anterior synechiae
Destruction of altered trabecular meshwork function by inflammatory mediators	Local inflammation and scarring
	Fibrous membrane contraction
	Posterior synechiae and pupillary block
	Initial fibrinous iridolenticular adhesions
	Later fibrous adhesions
	Anterior rotation of the ciliary body
	Inflammation of the posterior choroid/sclera
	Swelling or detachment of the ciliary body



A



B

FIGURE 26-1 Pathology of uveitis and glaucoma. (A) Infiltration of the trabecular meshwork and Schlemm's canal (S) can produce open-angle glaucoma. (B) Angle closure in a case of sarcoid uveitis. Note sarcoid nodule and iris adhesion to the peripheral cornea. (Courtesy of W. Richard Green, M.D.)

buildup of aqueous in the posterior chamber forces the peripheral iris forward (*iris bombe*), which obstructs the chamber angle and aqueous outflow. Because permanent anterior synechiae can result from prolonged contact of the iris and trabecular meshwork, early reversal of this pupillary block is necessary to prevent chronic angle-closure glaucoma, either by pharmacologically dilating the iris to break fibrinous posterior synechiae, or by peripheral iridotomy if irreversible pupillary block has already developed.

Posterior uveitis primarily causes glaucoma via its association with anterior uveitis. However inflammation of the choroid and posterior sclera can produce angle-closure glaucoma by causing swelling and detachment of the choroid or ciliary body. This leads to forward rotation of the latter and compression of peripheral iris against the trabecular meshwork.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Due to the proximity of the aqueous outflow channels, iridocyclitis is the ocular inflammation most likely to cause glaucoma. Predominant symptoms of iridocyclitis include pain and photophobia from contraction of the inflamed iris and ciliary body, and decreased vision due to anterior chamber cells and protein, endothelial deposits, cystoid macular

edema, and, occasionally, epithelial edema from elevated IOP (Table 26-3). Chronic, mild uveitis and intermittent, mild bouts of inflammation produce less dramatic symptoms, but are more likely to result in glaucomas due to the insidious development of anterior and posterior synechiae.

TABLE 26-3 DIAGNOSIS OF ANTERIOR UVEITIS (IRIDOCYCLITIS)

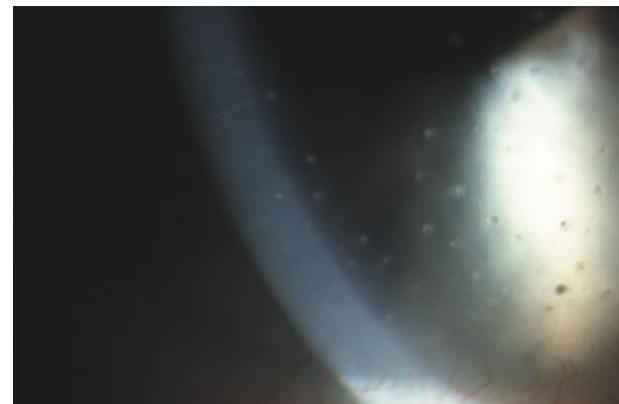
<i>Symptoms</i>	<i>Signs</i>
Pain	Ciliary flush
Photophobia	Anterior chamber flare, fibrin (severe cases)
Decreased vision	Anterior chamber circulating white blood cells
	Keratic precipitates
	Anterior synechiae
	Posterior synechiae
	Cystoid macular edema
	Decreased intraocular pressure
	Elevated intraocular pressure
	<i>Late findings:</i>
	Cataracts
	Band keratopathy
	Angle closure
	Glaucomatous optic nerve damage

Common signs of iridocyclitis include perlimbal injection (ciliary flush), circulating white blood cells, and cloudiness of the slit-lamp beam within the anterior chamber (flare) due to increased protein in the aqueous humor (Fig. 26–2A–F). Keratic precipitates, focal deposits of inflammatory cells on the corneal endothelium, are also commonly seen. Uveitis has historically been subdivided into granulomatous and nongranulomatous based on the size of the keratic precipitates, which were said to be large

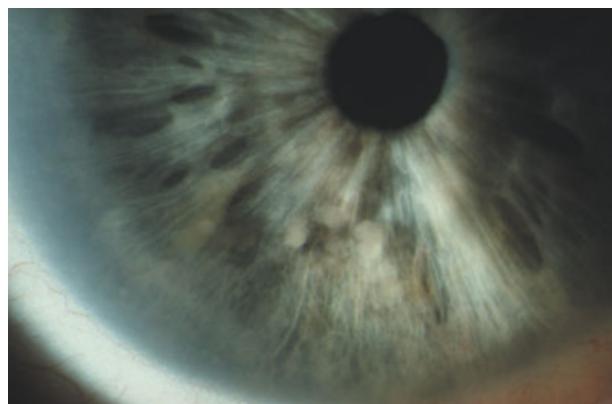
and “greasy” in the former condition (“mutton-fat KP”). However, this description is largely qualitative, with no absolute consensus as to a size or character of keratic precipitates that makes this distinction. Severe, exudative forms of uveitis may fill the anterior chamber with fibrin, suspending the cells in a plasmoid or “plastic” aqueous. Anterior synechiae are best appreciated by gonioscopy, along with irregular deposition of pigment and, occasionally, keratic precipitates, on the trabecular meshwork



A



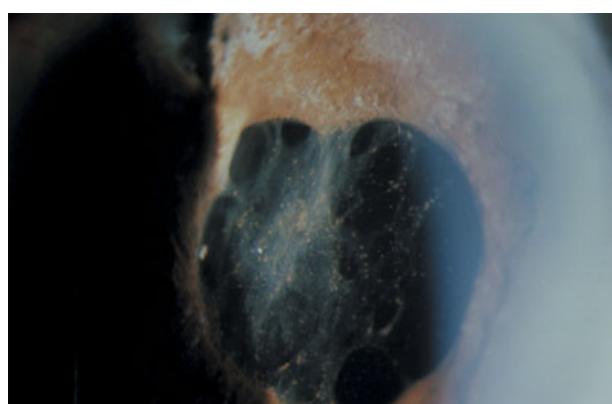
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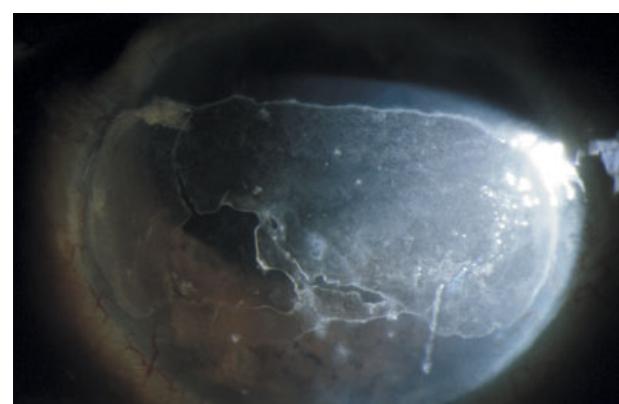
C



D



E



F

FIGURE 26-2 Typical signs of acute iridocyclitis include ciliary flush (A) and discrete keratic precipitates (B). Patients with granulomatous uveitis can develop iris nodules, either on the iris surface (C) or at the pupillary margin (D), termed Busacca and Koeppe nodules respectively. (E) Severe inflammation can produce fibrin in the anterior chamber and may lead to irreversible posterior synechiae unless treated aggressively with corticosteroids and pupillary dilation. (F) Band keratopathy may occur as a late sign of chronic uveitis and glaucoma. [(E) courtesy of Julia Whiteside-Michel, M.D.]

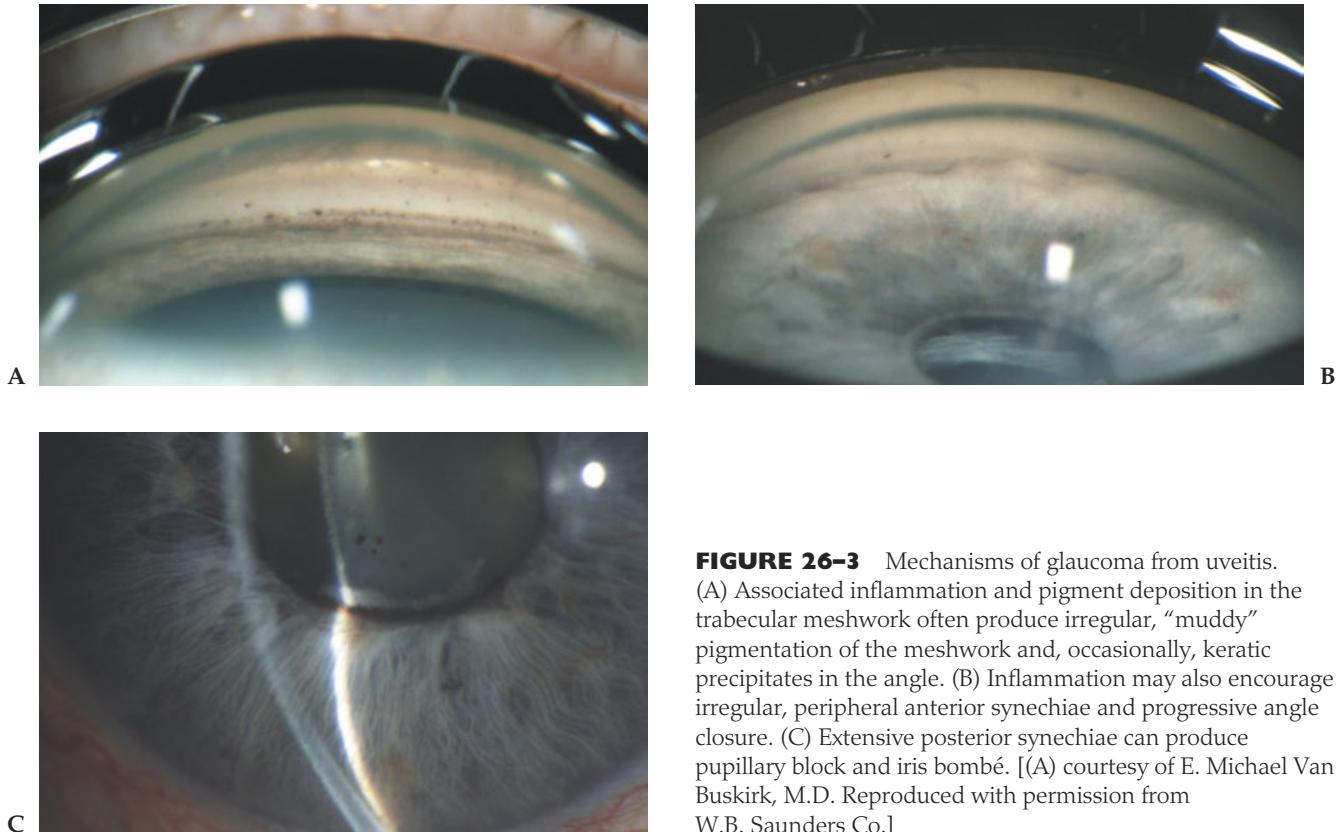


FIGURE 26-3 Mechanisms of glaucoma from uveitis. (A) Associated inflammation and pigment deposition in the trabecular meshwork often produce irregular, “muddy” pigmentation of the meshwork and, occasionally, keratic precipitates in the angle. (B) Inflammation may also encourage irregular, peripheral anterior synechiae and progressive angle closure. (C) Extensive posterior synechiae can produce pupillary block and iris bombé. [(A) courtesy of E. Michael Van Buskirk, M.D. Reproduced with permission from W.B. Saunders Co.]

(Fig. 26-3A–C). Direct biomicroscopy may reveal posterior synechiae, although their true extent may not appear until after pupillary dilation. Cataracts, cystoid macular edema and band keratopathy more commonly accompany chronic and recurrent uveitis.

Although IOP often falls in acute iridocyclitis, severe inflammation with marked cells and fibrin in the anterior chamber can produce elevated IOP that is reversible as long as the angle remains open. Irreversible glaucoma generally results from permanent trabecular damage or anterior chamber angle closure due to chronic, or repeated attacks of uveitis.

The optic nerve generally appears normal, although typical glaucomatous cupping and visual field loss can result from prolonged, unrecognized, or untreatable elevated IOP. Laboratory studies helpful in diagnosing and managing anterior uveitis generally depend on the clinical presentation.² The pattern of inflammation (for example, unilateral or bilateral, granulomatous or non-granulomatous) and the medical history will often direct the laboratory evaluation. If the presentation and history do not suggest a specific diagnosis, such as ankylosing spondylitis or Behcet’s disease, a limited search should be made for an “occult” systemic disease associated with the uveitis. This includes a chest x-ray for hilar adenopathy and a serologic study for syphilis.³ The value of additional tests, such as angiotensin converting enzyme levels, is limited by questions of sensitivity and specificity.²

Although other tests, such as computed tomography to check for hilar adenopathy, may be highly specific⁴ and more sensitive than a chest x-ray, cost considerations generally preclude their routine use.

As already noted, most forms of uveitis are probably immunologically mediated. Because the human leukocyte antigen (HLA) molecules markedly influence the immune response, one’s HLA genes can influence susceptibility to immune-mediated disease. Table 26-4 lists the known associations of several uveitic entities with HLA antigens. Although these correlations are not generally diagnostically useful, the association of HLA-B27 with ankylosing spondylitis or reactive arthritis is well known, and its presence occasionally aids the differential diagnosis of a patient with a unilateral, anterior uveitis.

TABLE 26-4 ASSOCIATION OF UVEITIS WITH HUMAN LEUKOCYTE ANTIGENS

B27	Ankylosing spondylitis Reactive arthritis Inflammatory bowel disease ^{*40} Psoriatic arthritis ^{*81}
DR4	Vogt-Koyanagi-Harada disease ⁸²
A29	Birdshot chorioretinopathy ⁸³
DR2	Pars planitis ⁸⁴
B51	Behcet’s disease ⁸⁵

* Less common.

OCULAR INFLAMMATORY CONDITIONS ASSOCIATED WITH GLAUCOMA

Table 26–5 lists the diseases most commonly associated with glaucoma, their contribution to uveitis in general, and their likelihood of involving glaucoma. This table and the following discussion retain the classification scheme used in Table 26–1 because most of these conditions involve the anterior uvea. However, primary involvement of other ocular structures can be an important key to diagnosis, and these are indicated in parentheses when necessary. Most of these conditions require nonspecific therapy, but some also respond to specific ocular and systemic treatments.

OCULAR SYNDROMES

Fuchs' Heterochromic Cyclitis

This condition, first described in 1906, consists of chronic, mild cyclitis and iris heterochromia frequently associated

with cataracts and, less commonly, with glaucoma.⁵ Fuchs' heterochromia occurs equally between men and women, generally in the third and fourth decades⁶ and can be more difficult to diagnose in blacks, who display more subtle iris changes.⁷

Fuchs' is likely an autoimmune disorder because some patients possess immune deposits in the iris stroma, and nearly 90% have serum antibodies against a corneal epithelial protein.⁸ This frequency is much higher than other observed associations, including heredity, sympathetic denervation, and degenerative factors.⁹

Because patients with Fuchs' heterochromia typically have few symptoms of anterior uveitis, those seeking attention generally have advanced disease. Presenting symptoms include decreased vision from cataract formation and concern about iris heterochromia.

Heterochromia results from progressive atrophy of the iris stroma, usually beginning at the pupillary margin and generally producing a lighter iris on the affected side

TABLE 26-5 UVEITIS AND GLAUCOMA: REPRESENTATIVE DISEASES

Diagnosis	Frequency in a Uveitis Clinic (%)	Prevalence of Glaucoma (%)
Ocular Syndromes		
Fuchs' cyclitis	2.5	20 ⁸⁶
Glaucomatocyclitis Crisis (Posner-Schlossman)	rare	100
Idiopathic uveitis	24.2	15
Lens-induced uveitis	rare	common
Pars planitis (pars plana, anterior vitreous)	9.8	6
Sympathetic ophthalmia (posterior uvea)	rare	43 ²⁴
Suspected Immune-related (systemic) Disease		
Juvenile rheumatoid arthritis	2.5	14 ⁸⁷
Ankylosing spondylitis	5.5	14
Reactive arthritis	7.2	14
Behçet's disease	0.4	19 ^{88*}
Inflammatory bowel disease	0.9	30
Psoriatic arthritis	1.3	19
Sarcoidosis (anterior and posterior uvea)	5.5	25
Scleritis (sclera, posterior uvea)	**	10 ⁹³
Vogt-Koyanagi-Harada (posterior uvea)	3.3 ⁹⁴	38 ⁸⁹
Infectious		
Toxoplasmosis (posterior uvea)	5.1	12 ⁹⁰
Congenital syphilis (interstitial keratitis)	1.7 ⁹⁴	28 ⁹¹
Herpes simplex (keratouveitis)	0.8 ⁹⁴	27 ⁹²
Herpes zoster (keratouveitis)		
Masquerade Syndromes		
Retinal detachment (Schwartz-Matsu)	rare	common
Ischemia	rare	common
Pigment dispersion	rare	common

Data based on the experience of the Casey Eye Institute Uveitis Clinic, Oregon Health and Science University, unless noted otherwise. The frequency of a given diagnosis should be extrapolated with caution because this depends on demographics, geographics, referral patterns, and numbers. Glaucoma prevalence varies with the definition of glaucoma and the duration of disease follow-up. Percentages are based on a referenced published series or the experience at Oregon Health and Science University, and should be taken as a representative study among a range of observations. The designation of glaucoma as "common" indicates that the authors concluded that glaucoma was frequently associated, but no series was sufficiently large to assign a specific percentage with confidence.

*Based on percent of eyes with "high intraocular pressure."

**Data unavailable

in patients with dark irides. In patients with light irides, the affected eye will be darker due to iris pigment epithelium showing through the atrophic stroma (Fig. 26-4A–D). Pathologically, stromal atrophy involves loss of melanocytes, decreased melanosome size, and hyalinization of the clinically exposed iris vessels.¹⁰

PEARL... Because heterochromia in Fuchs' results from atrophy of the iris stroma, the affected eye is typically lighter in patients with dark irides. However, in patients with light irides, this atrophy may expose the iris pigment epithelium and make the eye appear darker.

Signs of uveitis are subtle, with only minimal aqueous cells and flare. Distinct, fine stellate keratic precipitates, occasionally connected by fine filaments, are more widely distributed over the corneal endothelium compared with other uveitic entities (Fig. 26-4D). Small iris nodules, usually at the pupillary border, appear in approximately 20 to 30% of patients,⁷ and may aid diagnosis in patients with less obvious heterochromia. Posterior subcapsular cataracts, usually a result of chronic inflammation, are a late complication.

Classically, anterior and posterior synechiae do not develop. However, fine blood vessels may appear on the trabecular meshwork and can hemorrhage following acute decompression during intraocular surgery. The incidence of glaucoma varies with the duration of uveitis and generally results from inflammatory destruction of the anterior chamber angle, although rubeosis iridis and neovascular glaucoma have also been reported.¹¹

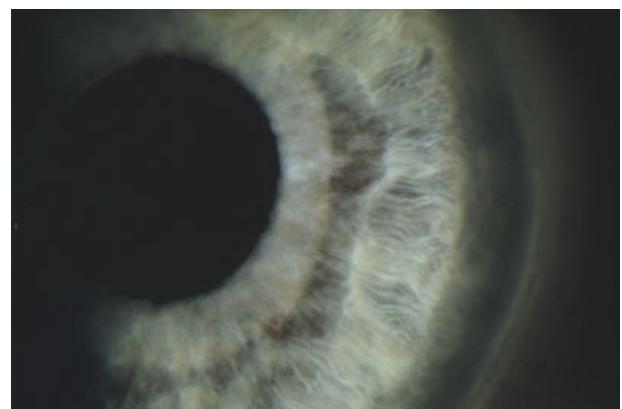
Fuchs' heterochromic cyclitis typically does not respond to corticosteroids, which may both accelerate cataract formation and induce glaucoma. Cataract extraction using modern techniques and posterior chamber lens implantation can provide good visual recovery, despite the risk of postoperative uveitis and glaucoma.¹² Glaucoma control generally relies on medical management, although filtration surgery with adjunctive antimetabolites is often necessary.¹³

Glaucomatocyclitic Crisis (Posner–Schlossman Syndrome)

Glaucomatocyclitic crisis typically consists of self-limited, unilateral, recurrent, mild attacks of anterior uveitis and highly elevated IOP.¹⁴ Patients generally are between 20



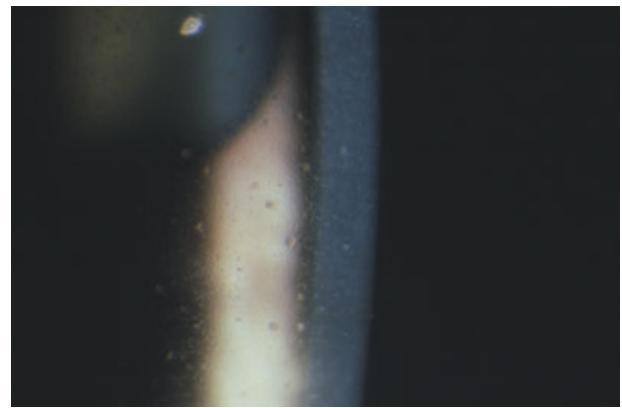
A



B



C



D

FIGURE 26-4 Features of Fuchs' heterochromic iridocyclitis. (A) Heterochromia results from thinning and atrophy of the iris stroma, well illustrated by comparing the (B) affected and (C) unaffected eyes with high magnification. This exposes the iris pigment epithelium and produces a darker appearance in patients with light irides. (D) Keratic precipitates typically have a fine, stellate appearance, best seen with retroillumination.

and 50 years of age and have relatively few symptoms, aside from mild discomfort during the attacks and blurred vision and haloes around lights from epithelial edema caused by the marked rise in pressure.

Although the etiology is unknown, allergic conditions, immune factors, and prostaglandins have all been implicated in glaucomatocyclitic crises.⁹ In some series, patients show an increased pressure response to corticosteroids, suggesting a possible association with chronic open-angle glaucoma.^{15,16}

The episodes of mild cyclitis may last hours to weeks, with minimal aqueous flare and occasional circulating cells. Similarly, keratic precipitates are small, discrete, and few in number, and the anterior chamber angle is open without posterior synechiae. Iris hypochromia may occur, but with much less frequency than in Fuchs' syndrome.¹⁷

SPECIAL CONSIDERATION

The extent of IOP elevation in glaucomatocyclitic crises typically exceeds the severity of the patient's symptoms and uveitis.

IOP elevation, between 40 and 60 mm Hg, is notably out of proportion to the patient's symptoms and the extent of the uveitis. The pressure rise generally accompanies the uveitis, and may result from trabecular inflammation,¹⁸ although a prostaglandin-mediated increase in aqueous humor production has also been suggested.¹⁹ Although IOP and aqueous humor dynamics usually return to normal between attacks, pressure can remain elevated in both eyes, further supporting an association with open-angle glaucoma in some cases.

Although corticosteroids may help control the inflammation of acute episodes, cyclitic attacks are generally self-limited,¹⁷ and chronic or prophylactic therapy is not necessary. The IOP usually responds to topical glaucoma agents that inhibit aqueous humor formation, although occasionally, severe cases with recurrent attacks and optic nerve damage may need filtration surgery.²⁰

Trabeculitis

This rare, bilateral glaucoma was originally described as a local inflammation of the trabecular meshwork.²¹ A true case of trabeculitis with little evidence of ciliary body inflammation may be confused with primary open-angle glaucoma, although gray to yellow precipitates on the trabecular meshwork are described, along with focal, attached peripheral anterior synechiae. However, trabecular meshwork inflammation is usually associated with other manifestations of anterior uveitis. This inflammation generally responds to topical corticosteroids and, if necessary, antiglaucoma agents. As with all other forms of anterior uveitis, recurrent attacks or unrecognized inflammation may lead to recalcitrant

glaucoma, either from trabecular dysfunction or permanent closure of the anterior chamber angle.²²

Lens-Induced Uveitis (see Chapter 25)

Alterations of the lens can induce uveitis through several mechanisms. Phacolytic glaucoma, the lens-induced uveitis most characteristically associated with glaucoma, involves rupture of a hypermature cataract, marked rise in pressure, and macrophages in the anterior chamber, which are attracted to a gamma crystallin in the lens.²³ This uveitis resolves with removal of the lens protein at the time of cataract surgery.²⁴ Ironically, the term *phacoanaphylaxis*, which implies a sudden, catastrophic immune response, is usually applied to a more indolent form of uveitis associated with a ruptured lens.

Pseudophakia is also frequently associated with uveitis and glaucoma. The differential diagnosis of uveitis after cataract surgery includes infection, liberated cortical material, mechanical irritation, a reaction to the foreign body, or a reactivation of prior inflammation resulting from surgical trauma.

Pars Planitis (Intermediate Uveitis, Chronic Cyclitis)

This predominantly bilateral, chronic inflammation of the pars plana, peripheral retina, and anterior vitreous primarily begins in teenagers and young adults. The etiology is unknown. Clinical findings include anterior vitreous cells with "snowbanking" over the pars plana, peripheral retinal vasculitis, and cystoid macular edema, which is the primary cause of vision loss. The anterior segment demonstrates mild cells and flare, posterior subcapsular cataracts, and rare synechiae. Glaucoma results from complications of chronic inflammation, including anterior synechiae, iris bombé with angle closure, and neovascular changes.^{25,26} Treatment primarily involves topical and periocular corticosteroids to minimize inflammation, whereas cases resistant to corticosteroids may require immunosuppressive agents and pars plana vitrectomy.²⁷ Some cases require specific medical, and even surgical, glaucoma therapy to protect the optic nerve.

Sympathetic Ophthalmia

Sympathetic ophthalmia results from exposure of uveal tissue to the immune system following ocular trauma or surgery. The inflammation is insidious but progressive, beginning within weeks in the injured, "inciting" eye, and usually occurring weeks to months later in the fellow, sympathizing eye. Histologically, the inflammation includes lymphocytic infiltration of the anterior and posterior uvea, along with variable eosinophils and plasma cells. Yellow, clinically visible Dalen-Fuchs nodules are sometimes apparent and consist of pigment-laden epithelioid cells at the level of the retinal pigment epithelium.

Glaucoma can commonly result from sympathetic ophthalmia, apparently from direct inflammation of the trabecular meshwork, and from angle closure caused by iris thickening and posterior synechiae.²⁸

In the past, preventing sympathetic ophthalmia relied on enucleating the inciting eye within 2 weeks of injury. However, because even severely traumatized eyes are now rarely enucleated at this stage, prevention requires prompt, meticulous closure of penetrating ocular injuries. Medical management generally requires long-term corticosteroids,²⁸ although systemic immunosuppressives may be helpful in resistant cases. Glaucoma management is similar to that outlined for other inflammatory glaucomas and angle closure.

SYSTEMIC INFLAMMATORY CONDITIONS ASSOCIATED WITH GLAUCOMA

Juvenile Rheumatoid Arthritis

At least three forms of juvenile rheumatoid arthritis (JRA) exist: systemic JRA (Still's disease), polyarticular JRA, and pauciarticular JRA. Because uveitis is much more common in pauciarticular JRA, patients with this condition are the most likely to develop glaucoma. Uveitis may occur in 80 to 90% of patients with pauciarticular JRA and can produce many of its vision-threatening complications.²⁹

Juvenile ankylosing spondylitis represents a subset of pauciarticular JRA. In contrast to the other variants of pauciarticular JRA, these patients are usually male and test negative for antinuclear antibodies (ANA). They have back pain and develop joint disease after age 12. Juvenile ankylosing spondylitis patients often are HLA-B27 positive and can have a sudden-onset, unilateral anterior uveitis identical to adults with ankylosing spondylitis.

Although generally rheumatoid factor negative, 70 to 90% of patients with JRA and uveitis will have positive antinuclear antibodies. Some reported cases are associated with HLA-DPw2 and HLA-DRw5.³⁰

Anterior uveitis in pauciarticular, ANA-positive JRA is bilateral and initially asymptomatic, with the typical findings of chronic flare, anterior chamber cells, and keratic precipitates.³⁰ Uveitis usually follows the arthritis by months to years, which often portends a mild course.³¹ In contrast, uveitis that precedes the arthritis often results in severe ocular complications and poor vision.⁹ Although arthritis typically diminishes with time, the iridocyclitis continues into adult life, with intermittent exacerbations and chronic flare.

Posterior synechiae are common, along with band keratopathy and cataracts, either from steroid therapy or from chronic inflammation. Posterior segment inflammation, when present, can produce macular edema, cyclitic and vitreous membranes, and traction retinal detachment. Glaucoma generally presents as acute angle closure, due to posterior synechiae, or chronic angle closure, which results from progressive, peripheral anterior synechiae.

Because the uveitis produces few ocular symptoms, patients with pauciarticular JRA should receive eye examinations every 3 months, particularly if the disease began

between the ages of 2 and 8. Older children with a positive rheumatoid factor and a symmetric polyarthritis have a much lower risk for iritis.

Optimum management requires thorough consultation and coordination among the patient, parents, pediatrician, rheumatologist, and ophthalmologist. Although oral corticosteroids often control both the arthritis and the uveitis, the severe systemic and ocular complications of these agents limit their use in young children. A stepladder approach, designed to minimize corticosteroid use, has been recommended for uveitis and includes topical and periocular corticosteroids, followed by nonsteroidal anti-inflammatory agents, limited systemic corticosteroids, and, if necessary, systemic immunosuppressive agents.^{32,33}

Prevention, primarily through aggressive control of uveitis, is the best treatment for glaucoma. Adjunctive measures include periodic dilation with daily tropicamide to prevent posterior synechiae, and laser iridotomy for iris bombe. Chronic glaucoma may require medical therapy with aqueous humor suppressants. In some patients, filtration surgery with antimetabolites or, occasionally, valve implantation is necessary, although both may fail due to inflammation and young patient age.

Cataract surgery following at least 3 months of controlled inflammation can be successful in JRA patients.³² Some advocate posterior capsulotomy and anterior vitrectomy to reduce the risk of developing a cyclitic membrane, which can lead to chronic hypotony. However, adult patients with cataract and JRA are increasingly undergoing cataract extraction with placement of a posterior chamber intraocular lens via an anterior surgical approach.^{34,35}

Ankylosing Spondylitis (Marie-Strumpell Disease)

Classically, ankylosing spondylitis affects young males by a 3:1 ratio and produces arthritis of the sacroiliac joints, although the spine, peripheral joints, and tendons are also commonly involved. Ninety percent of patients are HLA-B27 positive and approximately 20 to 40% of patients, almost always with the HLA-B27 antigen, experience sudden onset, episodic, unilateral anterior uveitis.³⁶ Some patients present with recurrent uveitis, which, in these cases, is more severe than the arthritis itself.³⁷⁻³⁹

PEARL... The strong association of HLA-B27 antigen with ankylosing spondylitis and reactive arthritis may be an important aid in the differential diagnosis of patients with unilateral anterior uveitis.

The anterior uveitis produces classic pain, and anterior chamber cells and flare, which can be severe. The uveitis generally responds well to topical corticosteroids. However, treatment, including pupillary dilation, must be prompt and aggressive because recurrent uveitis can produce anterior and posterior synechiae and chronic glaucoma.

The first episode of iritis in association with ankylosing spondylitis or reactive arthritis almost always reduces IOP in the affected eye. In our series, 14% of patients with

iritis and spondyloarthritis eventually developed glaucoma,⁴⁰ in contrast to increased IOP in 39% of HLA-B27 negative patients with iritis.³⁸

Reactive Arthritis (Reiter's Syndrome)

Classic reactive arthritis consists of urethritis, polyarthritis, conjunctivitis, and, occasionally, other mucocutaneous lesions.⁴¹ Patients are commonly young men, often demonstrating the HLA-B27 genotype. The disease may be triggered by gram-negative dysentery or nongonococcal urethritis. In the classic presentation,⁴² over 50% of cases develop mucopurulent papillary conjunctivitis, which is typically self-limited, whereas the anterior uveitis appears identical to that seen in ankylosing spondylitis. A limited reactive arthritis, such as a pauciarticular arthritis and a urethritis, is being increasingly recognized and is far more common than the classic triad.

Behçet's Disease

Behçet's disease includes oral and genital mucosal aphthous ulcers and recurrent ocular inflammation. Associated maladies consist of arthritis and numerous vascular complications from the underlying occlusive vasculitis, including thrombophlebitis and vascular obstruction in several organ systems.⁴³ The inflammation, usually bilateral, consists of recurrent attacks of anterior and posterior uveitis. Anterior uveitis may result in a sterile hypopyon and occasionally leads to glaucoma,⁴⁴ whereas severe retinal vasculitis and necrosis commonly cause blindness.⁴⁵ Initial treatment includes prednisone, although cyclosporine and other immunosuppressive agents are often necessary.⁴⁶

Inflammatory Bowel Disease

Uveitis affects roughly 2 to 9% of patients with the inflammatory bowel diseases ulcerative colitis and Crohn's disease. This form of uveitis has a more varied clinical presentation than that associated with either ankylosing spondylitis or reactive arthritis. Most patients are female, and the inflammation may be bilateral and posterior to the lens. Because it lasts longer, this uveitis is more commonly associated with glaucoma.

Psoriatic Arthritis

Approximately 10% of patients with the inflammatory skin disease psoriasis develop an associated arthritis, and 7% of these experience uveitis. The clinical features of this uveitis are similar to those associated with inflammatory bowel disease.

Sarcoidosis

Sarcoidosis is a multisystem, immunologic disease that predominantly affects young black adults. Although the characteristic, noncaseating granulomas most commonly affect the hilar region of the lungs, other systems, including skin, are also involved, and ocular disease occurs in nearly 50% of patients. Ocular disease can cause chorio-

retinitis, retinal periphlebitis, and optic neuritis as well as lacrimal gland enlargement. Anterior uveitis occurs in 25 to 50% of patients⁴⁷ and is the primary cause of glaucoma.

Characteristic findings of sarcoid uveitis include large, "mutton fat" keratic precipitates, iris nodules, and anterior and posterior synechiae. The small, white nodules may appear within the iris crypts or lie at the pupillary border, termed Busacca and Koeppe nodules, respectively, whereas other nodules can involve the anterior chamber angle (see Fig. 26–2C and D).⁴⁸

Glaucoma, a major prognostic factor for poor vision, can occur in 10 to 25% of patients.⁴⁹ We have noted ocular hypertension in 25 to 30% of patients with sarcoidosis and uveitis, as opposed to elevated pressure in approximately 15% of patients with idiopathic uveitis (Rosenbaum, unpublished observation). Glaucoma generally results from granulomatous infiltration of the chamber angle, anterior synechiae, and angle closure from posterior synechiae and pupillary membranes, as well as steroid use.

Diagnosis of systemic sarcoidosis relies heavily on finding hilar adenopathy by chest x-ray, and many accept the association of uveitis with symmetric hilar adenopathy as diagnostic of sarcoid.⁵⁰ Occasionally, computed tomography of the chest demonstrates adenopathy that is not apparent on a routine x-ray.⁴ If clinically indicated, biopsy of the skin, lymph nodes, mediastinum, lung, and even the conjunctiva can help confirm the diagnosis. Measurement of serum angiotensin converting enzyme can correlate with active disease and is helpful in monitoring the response to corticosteroid treatment.⁵¹ Although gallium scanning, serum lysozyme, and cutaneous anergy can also support the diagnosis, none is specific for sarcoidosis.

Corticosteroids work best in patients with iritis, and isolated ocular inflammation may respond to topical treatment alone. Patients with chronic uveitis or with significant systemic involvement, such as pulmonary or neurologic disease, may require oral corticosteroids or even immunosuppressives. Stubborn inflammation may confound attempts to withdraw corticosteroids in patients with steroid-induced glaucoma.

Glaucoma management begins with aqueous humor suppressants, although some patients eventually require filtration surgery with adjunctive antimetabolites. In others, iris bombé and posterior synechiae may necessitate laser iridotomy. A prolonged course of intense corticosteroid therapy should follow intraocular surgery in all of these patients because inflammation tends to persist.

Episcleritis and Scleritis

Episcleritis, an inflammation of unknown etiology, may be diffuse and simple, or localized and nodular. Diffuse episcleritis produces mild globe tenderness, discharge, and redness due to conjunctival and episcleral injection. Generally self-limited over days, these attacks tend to recur but gradually diminish in frequency, although nodular episcleritis may persist.

Glaucoma with episcleritis is uncommon.^{52,53} Mechanisms include steroid-induced glaucoma, open-angle

glaucoma, and, occasionally, an acute open-angle form of glaucoma where the infiltrated, edematous episclera produces both elevated episcleral venous pressure and edema of the trabecular meshwork. These latter patients have severe pain and decreased vision, although both the glaucoma and the inflammation respond well to intense topical corticosteroids. Topical or systemic nonsteroidal anti-inflammatory agents may help the patient avoid the prolonged use of topical corticosteroids.

In contrast, patients with scleritis suffer severe pain with inflammation, swelling, and destruction of the sclera. Highly associated with systemic connective tissue disease, this condition may involve either the anterior or the posterior sclera.

Anterior scleritis may be either diffuse or nodular, heralded more by pain than by inflammation. Less commonly, anterior scleritis occurs in a necrotizing form with marked inflammation and may culminate in tissue loss, uveitis, and glaucoma. Some cases of anterior necrotizing scleritis occur without inflammation, are closely associated with rheumatoid arthritis, and lead to necrosis of the sclera via an obliterative vasculitis (scleromalacia perforans).

Mechanisms of glaucoma with anterior scleritis consist of anterior uveitis, scleritis of the limbus and trabeculitis, episcleral vasculitis, and steroid-induced glaucoma. Rare outcomes of anterior scleritis include neovascular glaucoma and angle closure from pupillary block.

Posterior scleritis may also be diffuse, nodular, or destructive, although the distinction is not possible without ultrasonography. Depending on the location of the involved sclera, patients may present with cyclitis, choroiditis with exudative retinal detachment, or papilledema. Glaucoma from posterior scleritis generally results either from associated anterior uveitis or from angle closure due to anterior choroidal effusion and forward rotation of the ciliary body.

Treatment of glaucoma relies primarily on managing the underlying scleritis, generally with systemic nonsteroidal anti-inflammatory agents. Severe cases, such as necrotizing scleritis or those threatening the optic nerve, may require high-dose, prolonged corticosteroids with appropriate vigilance for steroid-induced glaucoma. Topical and occasionally oral aqueous humor suppressants may be indicated to protect the optic nerve while waiting for the inflammation to subside. Occasionally, the pressure may not normalize, necessitating prolonged glaucoma therapy, and, rarely, trabeculectomy through unaffected, healthy limbal tissue. Periorbital corticosteroid injections should generally be avoided in patients with scleritis because this may promote rupture of the globe. However, posterior scleritis is an exception to this rule.

Vogt-Koyanagi-Harada Syndrome

The Vogt-Koyanagi-Harada (VKH) syndrome primarily affects Asians, Hispanics, and Native Americans. It may produce eighth nerve disease, alopecia, vitiligo, and meningeal inflammation in addition to ocular abnormalities that include granulomatous anterior uveitis and posterior uveitis characterized by exudative retinal detachment.

Glaucoma in VKH results from both anterior segment inflammation and anterior chamber shallowing due to ciliary process inflammation and swelling and can be an early indication of this disease.^{54,55} VKH requires chronic corticosteroids and immunosuppressives. Medical therapy controls the glaucoma in some patients, although the majority require surgery.⁵⁴

INFECTIOUS CAUSES OF INFLAMMATION ASSOCIATED WITH GLAUCOMA

Rubella

Congenital rubella can affect nearly all parts of the eye. Glaucoma, associated with more severe disease, occurs in fewer than 15% of patients^{56,57} and may not develop until late childhood or early adulthood. Iridocyclitis can produce an acute, reversible glaucoma that responds best to corticosteroids and glaucoma medications. Irreversible glaucoma results from altered development of the anterior chamber angle, which resembles that of congenital glaucoma.

Mumps

Mumps can produce inflammation of several ocular structures and iritis, and though rare, may cause glaucoma.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) produces numerous ocular complications involving primarily the retina and optic nerve through several mechanisms, including direct viral infection, secondary infection with opportunistic organisms, and tumors. The reported glaucoma associated with HIV infection consists of bilateral angle closure with choroidal effusions and anterior rotation of the ciliary body. The best treatment outcome results from corticosteroids, cycloplegics, and aqueous humor suppressant therapy.^{58,59}

Hansen's Disease (Leprosy)

Hansen's disease, caused by infection with the acid-fast bacillus *Mycobacterium leprae*, occurs in lepromatous, borderline, and tuberculoid forms. Uveitis occurs in 5 to 20% of patients with leprosy, depending on the form, and can present with pathognomonic iris pearls or miliary lepromata, larger nodular lepromata, chronic iridocyclitis, and acute plastic iritis.⁶⁰ The incidence of glaucoma for all forms of leprosy is about 4%. It is 10% for patients with the lepromatous form, generally secondary to chronic iridocyclitis.^{61,62} In contrast, some eyes, particularly those with acute plastic iritis, demonstrate lower than normal IOP, probably due to decreased aqueous humor formation.⁶³ Although glaucoma treatment is similar to that described for other forms of inflammatory glaucoma, the uveitis itself may respond to dapsone and rifampin, as well as to corticosteroids.⁶⁰

Toxoplasmosis

Glaucoma, presumably secondary to iridocyclitis, can accompany active chorioretinitis from toxoplasmosis, along

with cataracts, band keratopathy, retinal detachment, and optic atrophy.⁶⁴ In a host with normal immunologic function, active toxoplasmosis is a unilateral disease, and elevated IOP almost invariably occurs in the affected eye.

Syphilis

Both acquired and congenital syphilis can produce anterior uveitis with occasional glaucoma. Adults with acquired syphilis may develop anterior uveitis with glaucoma during the secondary stage of the disease, along with rash and other associated findings.

Congenital Syphilis (Interstitial Keratitis)

In congenital syphilis, characteristic interstitial keratitis occurs in about 15% of cases and generally appears by age 5 to 16. Beginning often with unilateral lacrimation, photophobia, and pain, the condition usually progresses to bilateral pain, corneal edema, and infiltrates, frequent anterior uveitis, and deep corneal vascularization (salmon patches). The inflammation may last weeks to months, leaving persistent “ghost vessels” at the level of Descemet’s membrane (Fig. 26–5).

Glaucoma may result directly from iridocyclitis, or may appear later in life, often decades after the original inflammation is resolved. This delayed glaucoma may present with either an open or a closed angle.

The open-angle type of glaucoma is asymptomatic, with variable pigmentation and old anterior synechiae from the original inflammation, which may not be directly related to the pressure rise. A more occlusive glass membrane formation over the angle structures has also been described.⁶⁵ This glaucoma often requires filtration surgery.

Late-onset, closed-angle glaucoma primarily results in eyes with small anterior segments and shallow chambers, possibly a result of the interstitial keratitis. Inflammatory anterior synechiae, iris, and ciliary body cysts and lens dislocation may also contribute in certain cases. The glaucoma, which may be acute and symptomatic, or subacute with chronic angle closure, generally responds to peripheral iridectomy and medical therapy.^{66,67}

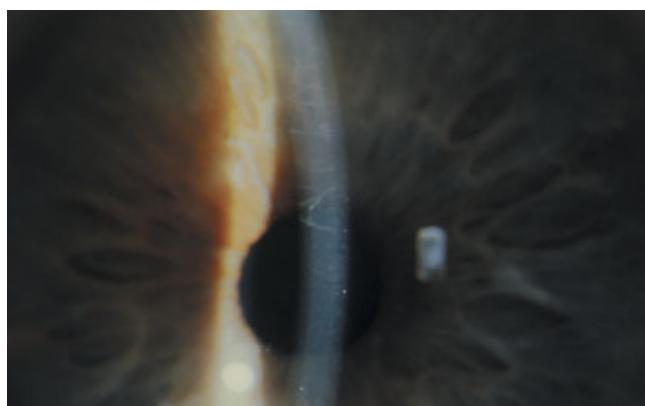


FIGURE 26–5 Residual “ghost vessels” from interstitial keratitis.

Herpes Simplex Keratouveitis

Herpes simplex keratouveitis occurs primarily in patients with secondary, or recurrent disease, and coincides with stromal keratitis, probably due to direct infection with the herpes virus.^{68,69} Glaucoma is intermittent and generally results from direct inflammation of the trabecular meshwork,⁷⁰ and angle closure in severe cases.⁷¹

PEARL... Patients with herpes simplex keratouveitis should have periodic intraocular pressure measurements because the glaucoma can be intermittent in this condition.

The treatment of glaucoma relies heavily on controlling the inflammation. This entails both specific treatment of the underlying infection, usually with trifluridine or acyclovir, and nonspecific control of inflammation with corticosteroids, which by themselves could reactivate epithelial disease if not used along with antivirals.

Some patients with herpes simplex keratouveitis require standard medical glaucoma management during active inflammation and, sometimes, even after the inflammation is resolved. Persistent, unresponsive glaucoma may ultimately require filtration surgery with adjunctive antimetabolites.⁷⁰

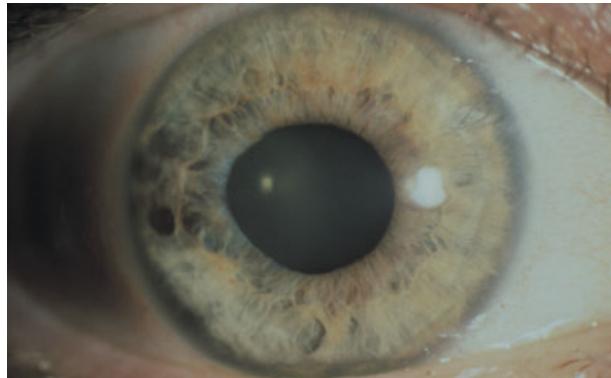
Herpes Zoster Keratouveitis

In herpes zoster ophthalmicus, the virus gains access to the eye via the ophthalmic branch of the trigeminal nerve, either as a primary infection or through reactivation of dormant virus residing in the gasserian ganglion. Ocular involvement often involves severe pain and a unilateral vesicular rash that usually affects the tip of the nose, indicating infection of the nasociliary branch of the ophthalmic nerve. Anterior ocular involvement consists of epithelial and stromal keratitis, which often permanently diminish corneal sensation, and uveitis consisting of severe inflammation, “mutton-fat” keratic precipitates, and iris atrophy with posterior synechiae (Fig. 26–6A,B). Glaucoma, generally from inflammatory mechanisms, occurs in approximately 30% of cases.^{68,72,73}

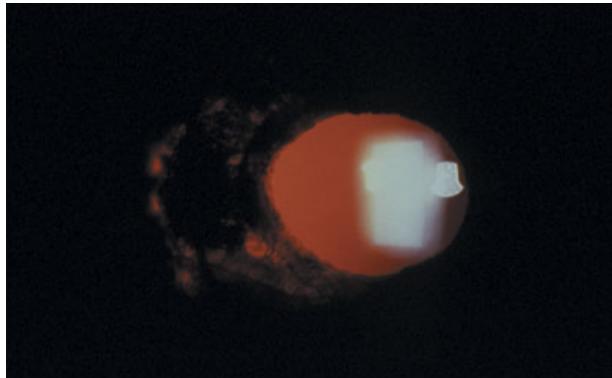
Early treatment with an oral antiviral, such as acyclovir, as soon as the cutaneous lesions develop, can minimize viral proliferation and limit ocular complications.⁷⁴ Adjunctive topical and, occasionally, periocular corticosteroids can help control intraocular inflammation and minimize the development of glaucoma. Medical and surgical management of the glaucoma itself may also be necessary, depending on the IOP and state of the optic nerve.

Acute Retinal Necrosis

Acute retinal necrosis (ARN) is a rapidly progressive retinitis secondary to a virus from the herpes family, usually varicella and sometimes herpes simplex. An occlusive retinal vasculopathy, its onset is sudden and is accompanied by redness, pain, and photophobia, with frequent



A



B

FIGURE 26-6 (A) Herpes zoster uveitis may result in sectoral iris atrophy, and (B) is more easily appreciated on iris transillumination. (Courtesy of Julia Whiteside-Michel, M.D.)

retinal detachment. IOP is almost always higher in the affected eye, often because of marked anterior segment involvement. Treatment should include an antiviral such as acyclovir, valacyclovir, or famciclovir. Although ARN can occur in normal hosts, immunocompromised patients are at greatest risk for developing viral retinitis.

MASQUERADE SYNDROMES

Some conditions such as lymphoma, leukemia, or retinitis pigmentosa may mimic uveitis and be mistaken for an inflammatory process. Three forms of these so-called masquerade syndromes are commonly associated with glaucoma.

Schwartz-Matsuo Syndrome (Retinal Detachment)

Although the majority of patients with a retinal detachment have normal or reduced IOP, ocular hypertension occurs in up to 13% of patients with retinal detachment.⁷⁵ Subsequent to the first description of this association by Schwartz,⁷⁶ Matsuo observed that photoreceptors in the aqueous humor of many of these patients can mimic leukocytes, simulating a uveitic process.⁷⁷ Although marked pressure elevation occurs in some patients, it resolves following successful retinal detachment surgery.

Pigment Dispersion Syndrome

Pigment dispersion results from the mechanical rubbing of lens zonules against the iris, releasing posterior pigment throughout the anterior and posterior chambers. The specifics of this condition and its associated glaucoma are discussed in Chapter 19. Circulating pigment in the anterior chamber can be mistaken for leukocytes.

Ocular Ischemia

Although a rare cause of uveitis,⁷⁸ ocular ischemia is often overlooked in the differential diagnosis. The typical patient is older and has evidence of vascular disease in other organs. The ischemic eye is usually painful with marked

anterior chamber flare. Intraretinal hemorrhage and rubesis iridis may also occur and lead to neovascular glaucoma.

MANAGEMENT OF INFLAMMATORY GLAUCOMA

Treatment of glaucoma from ocular inflammation relies on accurate diagnosis and aggressive management of the underlying condition. Specific glaucoma therapy may be required to prevent optic nerve damage while the inflammation resolves and may be necessary long term, depending on the extent of the damage to the aqueous outflow structures. Permanent, extensive damage occasionally necessitates surgical trabeculectomy, ideally only after inflammation is fully controlled.

Corticosteroids are the mainstay for treatment of ocular inflammation. Topical instillation of prednisolone acetate 1%, or dexamethasone phosphate 0.1%, every 1 to 2 hours generally provides adequate tissue levels to treat most cases of anterior uveitis, followed by tapering and eventual discontinuation of the drug as the inflammation subsides.

Periocular corticosteroid injection may be necessary in cases resistant to topical therapy. Although triamcinolone hexacetonide (40 mg/mL) is probably the most potent, longest-acting, locally injectable corticosteroid, it is also the preparation most likely to induce prolonged glaucoma and cause cutaneous atrophy. Fortunately, glaucoma is a very rare complication of corticosteroid injection if the patient has not developed glaucoma on topical corticosteroids and if the steroid is placed posteriorly.^{79,80} Betamethasone salts have a slightly shorter duration of action than triamcinolone, whereas dexamethasone is preferable if the clinician wishes to minimize potential long-lived effects from the injection.

PEARL... Periocular corticosteroid injections are contraindicated in patients with anterior scleritis.

Occasional severe cases may require oral corticosteroids or immunosuppressive agents. Although the latter may diminish total, chronic corticosteroid therapy, the potential for serious, life-threatening side effects dictates that they be used in conjunction with a physician familiar with their use and recommended monitoring.

An increase of IOP following institution of corticosteroids for inflammation may result from steroid response, but it is more likely due to recovery of aqueous humor formation following effective suppression of the inflammation. Although eliminating the corticosteroid, or substituting it with a weaker agent, can reverse a steroid response, the ongoing need to treat the inflammation may limit this approach. Ocular inflammation should never be undertreated out of concern for the possibility of a steroid response because active uveitis is more likely to produce elevated IOP and permanent destruction of the aqueous humor outflow pathways.

PEARL... Active ocular inflammation should always be aggressively treated with corticosteroids regardless of the intraocular pressure because glaucoma secondary to uveitis and its sequelae is more common than steroid-induced glaucoma.

Side effects of corticosteroids, including steroid-induced glaucoma and cataracts, can be minimized by selecting alternative, steroid-sparing strategies in specific conditions, such as nonsteroidal anti-inflammatory agents for scleritis, and immunosuppressive therapy for severe, chronic conditions such as rheumatoid arthritis. Corticosteroids should be avoided in conditions that generally do not respond well to these agents, such as Fuchs' heterochromia.

In addition to corticosteroids, chronic cycloplegia using atropine, homatropine, or scopolamine may help ameliorate inflammation by stabilizing the blood–aqueous barrier, improve patient comfort by relaxing ciliary spasm, and prevent posterior synechiae by encouraging pupillary dilation. Shorter-acting agents, such as cyclopentolate, and intermittent mydriatics like neosynephrine encourage pupillary mobility, further preventing permanent posterior synechiae.

Medical glaucoma therapy generally consists of topical, and occasionally oral, aqueous humor suppressants. Miotics may exacerbate inflammation, whereas stimulation and contraction of the ciliary muscle may shift the lens–iris diaphragm forward and exaggerate angle closure. Prostaglandin analogs should be used only sparingly because of their tendency to exacerbate inflammation.

If a secluded pupil and iris bombé do develop, bypassing the pupil with a peripheral iridotomy, using either the yttrium-aluminum-garnet (YAG) or argon laser, prior to development of permanent anterior syne-

chiae can reverse the angle closure and glaucoma. If performed in the presence of active inflammation, a patent iridotomy can be difficult to achieve and maintain, requiring intense topical corticosteroid therapy and close monitoring postoperatively.

Eyes with extensive peripheral anterior synechiae, angle closure, or permanent trabecular damage respond poorly to medical glaucoma therapy and generally require filtration surgery with adjunctive antimetabolites. Implantation of a valve, or seton, may be necessary in eyes where filtration surgery has failed. Because the extent of pressure lowering from these devices is generally less than with trabeculectomy, valves should be reserved for eyes with more than one failed filtration attempt.

Eyes in which antimetabolite filters and valves have failed to control IOP have a poor visual prognosis and may occasionally require cyclodestruction, either by transscleral YAG or diode laser. Generally more effective in the absence of total angle closure, this procedure should be considered a last resort because it may exacerbate the underlying inflammation, worsen vision, and might need to be repeated.

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RETINAL DISORDERS AND GLAUCOMA

Albert O. Edwards, M.D., Ph.D., and Yuri Ishihara, M.D.

Glaucoma interfaces with diseases of the retina and vitreous in several situations. These include the appearance of glaucoma in several retinal and vitreoretinal disorders, and retinal manifestations of specific glaucoma syndromes. Other, increasingly common, situations include the perioperative management of patients with glaucoma undergoing vitreoretinal surgery, and the problem of glaucoma developing after vitreoretinal surgery. Understanding these conditions and the nature of their association with glaucoma can aid the identification and timely management of these forms of glaucoma.

RETINAL DISORDERS WITH GLAUCOMA

Several vitreoretinal diseases may be complicated by glaucoma (Table 27-1). In general, these conditions are often heralded by either hypotony or ocular hypertension in one eye relative to the other.

CHOROIDAL MELANOMA AND OTHER INTRAOCULAR TUMORS

Intraocular tumors can produce either increased or decreased intraocular pressure (IOP). Although uveal melanoma is often initially associated with relative hypotony, subsequent growth of the tumor can lead to glaucoma through either open- or closed-angle mechanisms. The most common of these mechanisms are pigment dispersion and direct tumor invasion of the angle.¹ Other mechanisms include obstruction of the trabecular meshwork with the tumor and inflammatory cells, and angle closure from neovascularization, peripheral anterior synechiae, suprachoroidal hemorrhage, and mechanical effects of the tumor mass. Chapter 29 provides a complete discussion of the relationship of intraocular tumors and glaucoma.

SPECIAL CONSIDERATION

Several situations should prompt the clinician to search for a posterior segment cause of altered IOP, including

- Pressure change in one eye only
- Angle-closure glaucoma accompanied by normal anterior chamber depth of the fellow eye
- Decreased visual acuity days to weeks prior to the onset of pain
- History of prior retinal disease or surgery

MYOPIA

The relationship between refractive error and primary open-angle glaucoma is currently unclear. Although some studies of clinic patients have suggested a higher prevalence of open-angle glaucoma in myopes,² others do not support this association.³ Population-based surveys are similarly conflicting.^{4,5} Some studies suggest that glaucoma and myopia may not be linked through the prevalence of elevated IOP, but instead result from factors related to optic nerve susceptibility.⁶ These issues are also discussed in Chapter 1.

Myopic patients can have tilted discs and enlarged optic discs and cups, often with visual field defects similar to those seen in patients with glaucoma. All of these abnormalities can complicate the diagnosis of glaucoma and our ability to detect progressive glaucomatous optic nerve damage.

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration is a common disorder in which the late forms (geographic atrophy and exudation) affect approximately 7% of individuals over

TABLE 27-1 OVERVIEW OF RETINAL DISEASES THAT MAY BE COMPLICATED BY GLAUCOMA

Disease	Mechanism
Intraocular tumors	Open and/or closed angle
Myopia	Open angle
Age-related macular degeneration	Closed angle
Retinitis pigmentosa	Open and/or closed angle
Retinal syndromes	(Table 27-2)
Vitreoretinal syndromes	(Table 27-2)
Arteriovenous communication	Neovascular glaucoma
Coats' disease	Neovascular glaucoma
Choroidal hemangioma	Open and/or closed angle
Sturge-Weber syndrome	Congenital (early); open angle (later)
Diabetes mellitus	Open angle; Neovascular glaucoma
Retinal vein occlusion	Neovascular glaucoma
Retinal artery occlusion	Neovascular glaucoma
Retinopathy of prematurity	Closed angle (early and late)
Vitreous hemorrhage	Open angle
Retinal detachment	Open angle
Uveitis	Open and/or closed angle
Uveal effusion syndrome	Closed angle

the age of 75. Occasionally, exudation and a resulting chronic retinal detachment may lead to neovascular glaucoma (Fig. 27-1A,B).

Some patients with exudation experience massive vitreal, subretinal, or suprachoroidal hemorrhage leading to anterior displacement and rotation of the lens-iris diaphragm with angle-closure glaucoma. The majority of these patients are elderly, hypertensive, and on anticoagulants.⁷ Although the anticoagulant therapy may predispose these patients to massive posterior segment hemorrhage, the well-established benefit of these medications in treating systemic cardiovascular diseases, and the infrequency of this complication, suggest that medically indicated anticoagulant therapy should not be withheld from patients with exudative age-related macular degeneration.⁸

This condition is often temporary and may respond to medical treatment with aqueous humor suppressants and cycloplegia to reverse the angle-closure glaucoma. However, some patients will ultimately require enucleation for pain relief. Ghost cell glaucoma,⁹ another complication of vitreous hemorrhage from age-related macular degeneration, is discussed in Chapter 24.

RETINITIS PIGMENTOSA AND RETINAL AND VITREORETINAL SYNDROMES

The reported prevalence of primary open-angle glaucoma in patients with retinitis pigmentosa (RP) ranges from 2 to 12%,¹⁰ whereas that of primary angle-closure glaucoma in RP patients over the age of 40 is 1%.¹¹

These patients present both diagnostic and therapeutic challenges. In RP, visual field changes often start with midperipheral scotomata that evolve into a constricted central island of vision. These changes may mimic or obscure classic glaucomatous field loss. In addition, the waxy pallor of the optic disc in RP can obscure disc cupping and erosion (Fig. 27-2). Because these features may mimic glaucoma and make it difficult to detect progression, the practitioner may choose to treat IOP in patients with RP earlier and more aggressively than in patients without RP.

PITFALL... Patients with RP and glaucoma are challenging because early visual field loss can resemble that of glaucoma, and optic disc pallor may obscure glaucomatous cupping.

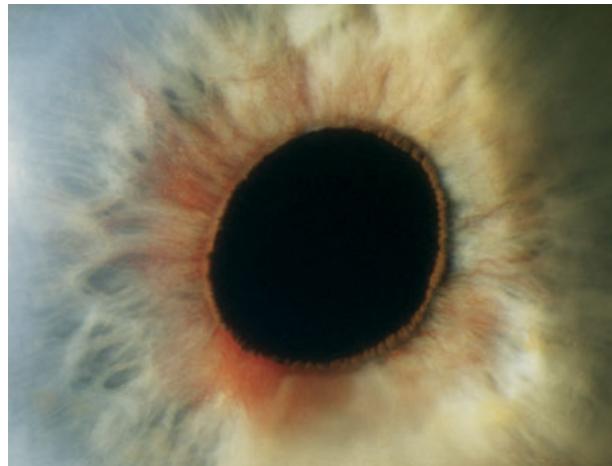
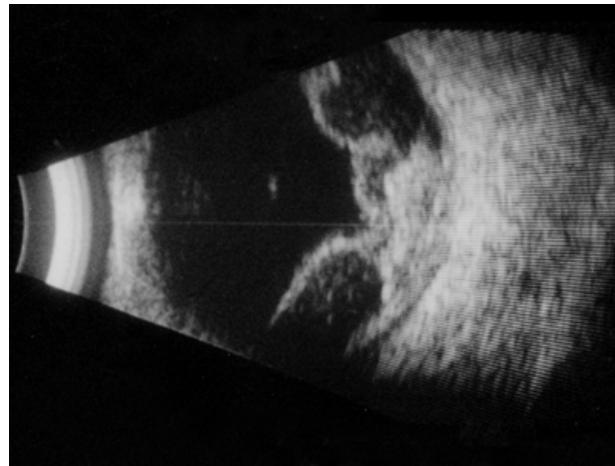
**A****B**

FIGURE 27-1 (A) Neovascular glaucoma secondary to chronic retinal detachment from peripheral subretinal hemorrhage. (B) Ultrasound demonstrates bullous detachment and underlying, dense irregular rubretinal disciform scar.

A number of syndromes involving retinal or vitreoretinal degeneration and glaucoma have been reported (Table 27-2). The most important of these is Stickler's syndrome, or hereditary arthro-ophthalmopathy. This condition is characterized by arthritis, cleft palate, mid-face hypoplasia, and ocular defects, which include radial perivascular lattice degeneration, vitreous degeneration, open-angle glaucoma, cataracts, and frequent retinal detachments. Mutations in the collagen 2A1 gene or collagen 11A1 can give rise to the classic vitreous defect of an optically empty vitreous cavity and vitreous membranes over the peripheral retina. These mutations can also produce a similar ocular phenotype that has a more visible, fibrillar vitreous.¹² The relative prevalence of glaucoma in these two genetic forms of ocular Stickler syndrome is unknown.



FIGURE 27-2 Retinitis pigmentosa and advanced glaucomatous optic nerve damage.

TABLE 27-2 HEREDITARY RETINAL AND VITREORETINAL SYNDROMES ASSOCIATED WITH GLAUCOMA

Disease	Mechanism
Retinal syndromes	
Aniridia	Angle-closure
Bilateral nanophthalmos, pigmentary retinal dystrophy, angle-closure glaucoma	Angle-closure
Microphtalmia with linear skin defects	Congenital
Muscle-eye-brain disease	Congenital
Retinal degeneration with nanophthalmos, cystic macular degeneration, and angle-closure glaucoma	Angle-closure
Vitreoretinal syndromes	
Norrie disease	Angle-closure
Retinal dysplasia	Angle-closure
Stickler syndrome (COL2A1)	Open angle
Stickler syndrome (COL11A1)	Open angle
Wagner disease	Open angle
Walker-Warburg syndrome	Congenital

ARTERIOVENOUS COMMUNICATIONS

Neovascular glaucoma has been reported as a complication of congenital arteriovenous communication of the retina. The mechanism appears to be related to retinal ischemia.¹³

COATS' DISEASE

Congenital retinal telangiectasia, or Coats' disease, is a retinal vascular disorder that primarily affects young, male children and is characterized by retinal telangiectasia and characteristic intraretinal exudates. This disease is in the differential diagnosis of leukocoria in a child and may lead to secondary angle-closure glaucoma by neovascular or

inflammatory mechanisms. The intravitreal exudates may lead to total retinal detachment, which can limit attempts to treat the retinal ischemia with panretinal photocoagulation (PRP). As a result, many of these eyes ultimately require enucleation.^{14,15}

CHOROIDAL HEMANGIOMAS AND STURGE-WEBER SYNDROME

Secondary glaucoma is not uncommon in patients with choroidal hemangiomas and choroidal hemorrhage. The most common mechanisms include neovascular glaucoma from retinal ischemia secondary to total retinal detachment, and angle closure due to choroidal effusion.

Sturge-Weber syndrome, a common cause of choroidal hemangiomas, is characterized by the combination of ocular, central nervous system, and skin hemangiomas. The classic facial cutaneous angioma or nevus flammeus, also known as a port wine stain, is usually present at birth and is most often unilateral. Ocular findings include glaucoma, episcleral hemangioma, diffuse choroidal hemangioma, and peripheral retinal venous tortuosity.

Thirty to 50% of patients with Sturge-Weber syndrome may develop glaucoma, and case series suggest that 60% of these are congenital, with 40% having a juvenile or adult onset.¹⁶ Glaucoma in infancy appears to result from abnormal development of the anterior chamber angle, similar to that of other congenital forms of glaucoma. Later-onset glaucoma generally has an open angle and increased episcleral venous pressure and can be associated with supraciliary effusion, also discussed in Chapter 23.¹⁷ It is most commonly of juvenile onset and progressive and has led to total blindness in patients in which it was not detected.¹⁸ Sturge-Weber syndrome is fully discussed in Chapters 23 and 30.

DIABETES MELLITUS AND OPEN-ANGLE GLAUCOMA

Several large epidemiological studies have addressed the association between diabetes and primary open-angle glaucoma.¹⁹ The results are controversial, and the epidemiology of this question appears in Chapter 1.

Some eyes with unilateral glaucoma show less severe diabetic retinopathy than in the fellow eye.²⁰ This suggests that open-angle glaucoma may somehow decrease the severity of diabetic retinopathy. This observation may be related to the underlying pathophysiology of diabetic retinopathy, although its significance is currently unknown.

CENTRAL RETINAL VEIN OCCLUSION

Patients with central retinal vein occlusion have an approximately 20% risk of developing neovascular glau-

coma, primarily due to the development of retinal ischemia. The pathogenesis, diagnosis, and management of these patients, along with the recommendations of the Central Retinal Vein Occlusion Study,^{21,22} are fully discussed in Chapter 21.

Case-control, incidence, and population studies have consistently found primary open-angle glaucoma to be a risk factor for central and branch retinal vein occlusions. The Eye Disease Case-Control Study Group reported an odds ratio of 5:4 for central retinal vein occlusion in patients with glaucoma, compared with those without glaucoma.²³ Development of a retinal vein occlusion should always alert the clinician to the possibility of underlying primary open-angle glaucoma.

In rare cases, eyes with central retinal vein occlusion can develop a reversible form of angle-closure glaucoma without iris or angle neovascularization. These patients present with pain or decreased vision days to weeks after the vein occlusion, an absence of peripheral anterior synechiae, and a normal angle in the fellow eye.^{24,25}

Although the exact mechanism of this angle closure is uncertain, supraciliary effusion, congestion of the ciliary body, and increased posterior segment volume may all contribute. Management of this condition includes topical and oral corticosteroids, aqueous suppressants, and cycloplegics.

CENTRAL RETINAL ARTERY OCCLUSIONS AND CAROTID OCCLUSIVE DISEASE

Neovascular glaucoma occurs in approximately 15% of patients with central retinal artery occlusion, nearly always within 12 weeks of the occlusive event.²⁶

The mechanism of anterior segment neovascularization following central retinal artery occlusion remains controversial. Although these patients clearly have altered retinal perfusion, it can be difficult to exclude a concomitant ophthalmic artery occlusion, and ocular ischemia. This may help explain the limited success of PRP in preventing neovascular glaucoma in this setting; in one prospective study, five of six patients with neovascularization of the iris developed neovascular glaucoma in spite of PRP.²⁶

Survival appears to be decreased in persons with a central retinal artery occlusion. Because of this, some authors suggest that these patients undergo a systemic evaluation for collagen-vascular and cardiovascular disorders.²⁷

RETINOPATHY OF PREMATURITY

In recent years, the advent of improved neonatal care and the development of cryotherapy and laser photocoagulation has significantly decreased the incidence of blindness from retinopathy of prematurity (ROP).²⁸ However, visual loss continues to occur, and secondary glaucoma is common (Fig. 27-3).

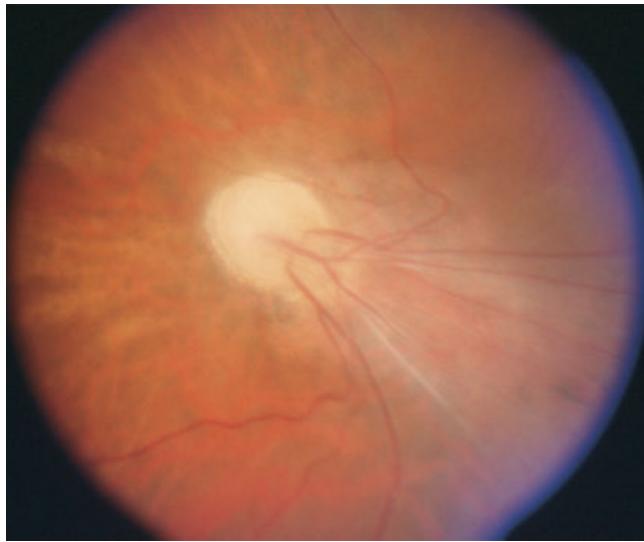


FIGURE 27-3 Fundus appearance of adult with retinopathy of prematurity who required an extracapsular cataract extraction for a mature cataract and angle closure. Note macular distortion and pale, cupped optic nerve.

Thirty percent of eyes with severe ROP may develop angle-closure glaucoma. Although angle closure can occur during the cicatricial phase of ROP, it often presents after the age of 2.²⁹ Late-onset angle-closure glaucoma has been reported in patients ranging from 12 to 45 years of age,³⁰ suggesting that these patients have a lifelong risk for this complication.

PEARL... Patients with retinopathy of prematurity have a lifelong risk of developing angle-closure glaucoma.

Angle closure in ROP patients probably results from cicatrization of the anterior vitreous and forward rotation of the ciliary body,³¹ as well as anterior displacement of the relatively large infant lens. Regardless of the mechanism, this glaucoma may present chronically or acutely. Although some cases respond well to medical management and peripheral iridectomy, definitive management usually requires a lensectomy, by either a pars plana or a limbal approach, often with subtotal vitrectomy.

Angle-closure glaucoma can also complicate surgical procedures for ROP. This generally results from inflammatory processes leading to extensive peripheral anterior synechiae or neovascular glaucoma in eyes with total retinal detachment. Management of these eyes includes trabeculectomy, ciliary body ablation, or endocyclophotoablation, depending on visual function, the status of the posterior segment, and the condition of the fellow eye.

VITREOUS HEMORRHAGE

Vitreous hemorrhage may occur in patients with diabetic retinopathy, occlusive vascular diseases, posterior vitreous separation with or without retinal tears, and a number of less common conditions, such as macroaneurysms, age-related macular degeneration, and subarachnoid hemorrhage. Open-angle glaucoma related to vitreous hemorrhage appears to be relatively uncommon and generally presents in one of three forms: ghost cell glaucoma, hemolytic glaucoma, and hemosiderotic glaucoma.³²⁻³⁶ These conditions are discussed in Chapter 24.

RHEGMA TOGENOUS RETINAL DETACHMENT

A rhegmatogenous retinal detachment commonly produces mild hypotony, presumably secondary to increased uveoscleral outflow through the retinal break. However, patients can occasionally present with unilateral elevation of IOP and an open angle. Pressure elevation appears to result from obstruction of the trabecular meshwork by photoreceptor outer segments, whose appearance in the anterior chamber resembles iridocyclitis.³⁷

This situation, referred to as the Schwartz syndrome, includes apparent iridocyclitis and normalization of the IOP following retinal detachment repair.³⁸ It may occur in 2% of patients with a rhegmatogenous detachment.³⁹ Management of this syndrome involves aqueous suppression and repair of the retinal detachment. In most cases, the glaucoma medications may be discontinued within a few weeks after the retina is successfully reattached.

UVEITIS AND OCULAR INFLAMMATION

Uveitis (discussed in Chapter 26) may produce either elevated or depressed IOPs. Elevated IOP in the setting of acute iridocyclitis may result from obstruction of the trabecular meshwork, angle closure due to peripheral anterior synechiae and neovascularization, or pupillary block from posterior synechiae and forward rotation of the ciliary body. Relative hypotony is generally due to increased uveoscleral outflow, decreased aqueous production secondary to cellular infiltration of the ciliary body, or tractive membranes causing ciliary body detachment. Chapter 27 discusses numerous causes of these conditions, their relationship to glaucoma, and its management.

UVEAL EFFUSION SYNDROME

The uveal effusion syndrome is characterized by choroidal effusion and nonrhegmatogenous retinal detachments. It is most likely to occur following surgery in nanophthalmic

eyes, which are of normal shape but abnormally small and hyperopic. In one report, reduced visual acuity due to postoperative complications occurred in 13 of 15 nanophthalmic patients.⁴⁰ Because of the increased potential for postoperative complications, including angle-closure glaucoma, malignant glaucoma (ciliary block), and suprachoroidal hemorrhages, intraocular surgery should be avoided in these patients whenever possible.

Management of angle-closure glaucoma is complicated and may include aqueous suppressants, laser iridotomies, peripheral pupillary iridoplasty and, rarely, mydriatics with careful gonioscopic assessment of their efficacy. The choroidal effusion and exudative retinal detachments have been successfully treated by some surgeons with vortex vein decompression or by creating scleral windows in the abnormally thickened sclera.⁴¹

GLAUCOMAS WITH RETINAL MANIFESTATIONS

PIGMENT DISPERSION SYNDROME

Pigment dispersion syndrome (see also Chapter 19) is a common form of secondary glaucoma, accounting for 1 to 1.5% of glaucoma in the Western world.^{42,43} In addition to glaucoma, patients with pigment dispersion syndrome appear to have an increased incidence of lattice degeneration and retinal detachment. One study has found lattice degeneration in at least one eye of 20% of 60 consecutive patients with pigment dispersion syndrome.⁴⁴ This prevalence was significantly higher than that reported for lattice degeneration overall.⁴⁵ The risk of retinal detachment in pigment dispersion syndrome ranges from 3 to 12%. Patients with this syndrome require careful evaluation of the peripheral retina and treatment of any suspicious lesions, especially prior to beginning miotic therapy.⁴⁶

MANAGEMENT OF THE GLAUCOMA PATIENT WHO REQUIRES RETINAL AND VITREOUS SURGERY

Vitreoretinal surgery in patients with glaucoma presents a complex series of management decisions. The surgeon must consider the absolute level of IOP and its duration, the patient's medications, the extent of optic nerve damage, the type and mechanism of glaucoma, the presence or absence of a filter or seton, and the anticipated future management of the patient's glaucoma.

In some patients, co-management of the glaucoma at the time of vitreoretinal surgery may be indicated. In others, the surgeon may defer surgical treatment of the glaucoma, and consider the impact of conjunctival scar-

ring from the retina procedure on the future ability of the glaucoma surgeon to perform a trabeculectomy.

PATIENTS WITH PROLONGED INTRAOOCULAR PRESSURE ELEVATION

Patients with chronic and significant IOP elevation prior to surgery are at increased risk for suprachoroidal hemorrhage. Because sudden decompression of the eye may predispose to such an event, the IOP should be controlled prior to surgery whenever possible, and relative hypotony should be avoided in the postoperative setting.

PATIENTS WITH SEVERE GLAUCOMA AND ADVANCED OPTIC NERVE DAMAGE

Elevated IOP commonly follows vitreoretinal surgery. It may also occur during the surgical procedure, either during routine manipulation of the globe, or as a deliberate break maneuver by the surgeon to achieve hemostasis. The surgeon should always minimize these pressure elevations, especially when operating on patients with extensive optic nerve damage. Potential maneuvers include using nonexpansile concentrations of intraocular gas; removal of all vitreous hemorrhage, especially blood contained within the vitreous base; and the use of ocular hypotensive agents in the postoperative setting. Early postoperative follow-up, with a paracentesis or removal of intraocular gas, may also be indicated.

MANAGEMENT OF GLAUCOMA DURING VITREORETINAL SURGERY

Patients with inadequate preoperative IOP control may occasionally require adjunctive glaucoma procedures at the time of vitrectomy and/or scleral buckling to protect the optic nerve. These methods include trabeculectomy, peripheral iridectomy, aqueous shunt placement, or endolaser photocoagulation of ciliary body processes. Setons specifically designed for insertion at the pars plana can provide successful control of glaucoma.⁴⁷ Transpupillary, trans pars plana, and endoscopic photocoagulation of 180 to 240 degrees of the ciliary body processes may also be valuable in these patients.^{48,49} Of these, endocyclophotocoagulation may be the safest because the ciliary processes can be directly visualized and treated.

Although filtration surgery and aqueous shunts can effectively control postoperative IOP, both procedures carry a higher risk of suprachoroidal effusion and hemorrhage when performed in conjunction with vitrectomy than when deferred to a later date. Although safer in this regard, endocyclophotocoagulation can produce macular edema and should be used with caution in patients with good central acuity.

MANAGEMENT OF PATIENTS WITH AN EXISTING TRABECULECTOMY OR AQUEOUS SHUNT

Many surgeons will avoid the trabeculectomy site at the time of a scleral buckle or vitrectomy by placing the peritomy as far from the filter as possible. Alternatively, a nonencircling scleral buckling procedure may help limit conjunctival dissection. Other steps that may help preserve bleb function include using viscoelastic in the anterior chamber to decrease fluid flow through the trabeculectomy, meticulous closure of the conjunctiva, and intensive postoperative corticosteroid therapy.

It is unknown whether a vitrectomy or scleral buckling procedure is more detrimental to a trabeculectomy. Although a vitrectomy is usually less likely to disturb the conjunctiva, the intraocular fluid flow and pressure alterations may also affect filtration. In one study, six of 16 blebs > 6 weeks old maintained function following vitrectomy. However, out of seven blebs < six weeks old, only one survived.⁵⁰ Although this suggests that mature blebs may be more likely to tolerate vitreoretinal surgery, the eyes with immature blebs also tended to have more severe disease.

Because pneumatic retinopexy decreases the need for conjunctival dissection, this procedure may be an appropriate alternative in patients who require retinal detachment surgery. In patients with aqueous shunts, manipulation of the globe during any retinal surgery may displace the tube, and its position should always be verified at the end of the case.

VITREORETINAL SURGERY IN THE PATIENT THAT MAY NEED A SUBSEQUENT FILTERING PROCEDURE

Some surgeons will modify the conjunctival peritomy during a scleral buckling or vitrectomy procedure to minimize conjunctival scarring in the superior quadrants. This involves placing the vitrectomy ports below the horizontal meridian, limiting the conjunctival peritomy for a scleral buckle to 1 to 3 quadrants, and sparing the superior conjunctiva. The advantages of these modifications are not well understood. Some of these patients may benefit from either endoscopic or trans pars plana photocoagulation of the ciliary processes at the time of surgery.

VITREORETINAL COMPLICATIONS OF GLAUCOMA THERAPY

Medical and surgical glaucoma therapy can produce several severe complications that involve the retina and vitreous. These include retinal detachments from the

use of strong miotics, and malignant glaucoma following glaucoma surgery in susceptible patients. Other complications of filtration surgery include endophthalmitis, vitreous loss, and retinal detachments, as well as hypotony and its associated choroidal effusions, maculopathy, and suprachoroidal hemorrhages. Chapter 43 contains a complete discussion of the complications of filtration surgery.

GLAUCOMA FOLLOWING VITREORETINAL SURGERY

Elevated IOP commonly follows vitreoretinal surgery and may occur through either open- or closed-angle mechanisms (Table 27-3). Although neovascular glaucoma was once a common cause of glaucoma following vitrectomy, increased use of adjunctive procedures accounts for an ever-widening variety of glaucomas in this setting. These procedures include the use of intraocular gases, silicone oil, perfluorocarbons, scleral buckling, and PRP.

GLAUCOMA FOLLOWING PARS PLANA VITRECTOMY

Acute postoperative glaucoma occurs in one third of patients undergoing pars plana vitrectomy. Although some glaucoma may result from the vitrectomy itself, adjunctive surgical procedures such as lensectomy,

TABLE 27-3 CAUSES OF GLAUCOMA FOLLOWING VITREORETINAL SURGERY

Cause	Mechanism
Vitrectomy	Trabecular meshwork obstruction by red cells, inflammatory, and lenticular debris
Neovascular glaucoma	Open and closed angle
Intraocular gas	Scleral expansion Pupillary block
Silicone oil	Trabecular meshwork obstruction by emulsified oil and cellular debris Pupillary block and filling of the anterior chamber with oil
Perfluorocarbon liquids	Angle closure Pupillary block (with silicone oil)
Scleral buckling procedures	Angle closure from supraciliary effusion, edema, and anterior rotation of the ciliary body
Panretinal photocoagulation	Angle closure from supraciliary effusion, edema, and anterior rotation of the ciliary body

intraocular gas infusion, and silicone oil injection account for an increasing percentage of this form of glaucoma.

The pars plana vitrectomy procedure itself is an uncommon cause of chronic postoperative glaucoma. Fewer than 10% of patients will develop an acute glaucoma from obstruction of the trabecular meshwork by erythrocytic, inflammatory, or lenticular debris.⁵¹ At one time, neovascular glaucoma, discussed below, was the most common type of early postoperative glaucoma following pars plana vitrectomy for diabetic and other ischemic retinopathies.^{52,53}

Erythroclastic and inflammatory glaucoma can usually be managed with aqueous suppressants and topical corticosteroids. Patients with significant residual or recurrent vitreous hemorrhage may develop ghost cell glaucoma and may require repeat vitrectomy with removal of the red blood cell debris. Fibrin may form across the pupillary space, especially in aphakic patients, on the surface of a gas bubble or silicone oil bubble. This complication is more likely in patients who have undergone extensive retinal photocoagulation and may be managed by creation of a hole in the membrane with a needle or the yttrium-aluminum-garnet (YAG) laser, or by injection of 25 µg of tissue plasminogen activator into the anterior segment.^{54,55} These patients require frequent follow-up because these membranes may recur.

NEOVASCULAR GLAUCOMA

Neovascular glaucoma primarily results from complications following vitrectomy for severe diabetic retinopathy. At one time, neovascular glaucoma occurred in as many as one fifth of patients. However, modern techniques and PRP have reduced the incidence of neovascular glaucoma to approximately 5% of diabetic patients following vitrectomy.^{52,53} In one study, 8.5% of eyes with proliferative diabetic retinopathy developed new stromal iris rubeosis after vitrectomy, and only 5% of eyes went on to develop neovascular glaucoma.⁵³ On the other hand, 57% of eyes with preexisting iris rubeosis showed regression following the surgery.

Retinal detachment, either from anterior hyaloidal proliferation or retinal breaks, is the major risk factor for neovascular glaucoma following vitrectomy in diabetic patients.^{56,57} In these cases, successful reattachment of the retina leads to regression of the iris neovascularization.⁵⁸ It is controversial whether lensectomy at the time of vitrectomy increases the risk of iris neovascularization and glaucoma.⁵⁹⁻⁶¹

INTRAOCULAR GAS

Air, sulfur hexafluoride (SF_6), and perfluorocarbons such as perfluoropropane (C_3F_8), are routinely used for intra-

ocular tamponade following vitrectomy, pneumatic retinopexy, and scleral buckling. The use of these intraocular gases has greatly improved the success of retinal detachment surgery; however, they may also produce glaucoma in the early postoperative period.

Twenty percent SF_6 and 16% C_3F_8 are considered nonexpansile concentrations of gas. However, even these concentrations can produce acute IOP elevation in one fourth of patients after vitrectomy.⁶² When higher concentrations are used, these gases expand at a rapid rate in the first 12 hours, and then more slowly over the next 36 hours. Pure (100%) SF_6 and C_3F_8 expand three-fold and fourfold over approximately 48 and 96 hours, respectively.⁶³ Although injection of 0.3 mL of C_3F_8 can acutely elevate IOP, this is usually well tolerated in the nonglaucomatous eye, which allows rapid outflow of intraocular fluid through the chamber angle.⁶⁴ However, injection of large volumes of gas (for example, 1 mL) may result in central retinal artery occlusions and severe visual loss.^{65,66}

Intraocular gas causes glaucoma by two mechanisms: scleral expansion and pupillary block. Expansion, which leads to an increased transscleral pressure gradient, occurs by uptake of nitrogen from surrounding tissue or by lowering of the external ocular pressure, such as during air travel. If the patient's head is positioned such that the anterior chamber is filled with aqueous, the expansion can be accommodated by aqueous outflow over several minutes. On the other hand, in phakic patients in the supine position, or in aphakic eyes with gas in the anterior chamber, aqueous cannot easily gain access to the anterior chamber angle, and IOP will remain elevated.

Pupillary block can occur when patients in the supine position develop apposition of the pupil to the anterior surface of the gas bubble. This is generally released by placing the patient in a prone position. Pupillary block may also result from fibrin growing on the surface of an intraocular gas or silicone oil bubble.

Air travel, mountain travel, hyperbaric treatment, and scuba diving all pose a significant risk for central retinal artery occlusion and severe pain from expansion of intraocular gases. During air or mountain travel, the external pressure decreases as a function of altitude, and, in the case of air travel, cabin pressure. This results in an increased intrascleral gradient, which is instantaneous.⁶⁷ Although choroidal compression and scleral expansion accommodate a significant portion of this increased pressure within seconds, subsequent normalization of IOP must occur through aqueous outflow.

The amount of intraocular gas that is safe for air travel is largely a function of the final minimum cabin pressure, which varies by aircraft design and altitude. For example, a Boeing 747 airliner flying at 37,000 feet

would experience decompression to 5600 feet in the cabin,⁶⁸ which allows a 25% expansion of an intraocular gas bubble. Some authors recommend that it is safe for patients to travel on commercial airlines with a 10% (0.6 mL) gas fill.⁶⁸ However, others suggest that larger gas volumes are still safe.⁶⁹ The use of aqueous suppressants prior to air or mountain travel is not recommended because a preflight, 5 mm Hg lowering of IOP would be insignificant compared with the nearly 200 mm Hg increase that occurs during decompression to 8,000 feet.^{67,68} Furthermore, aqueous suppressants could prolong the hypotony that occurs following the return to sea level, leading to uveal effusion and other ocular complications.

Intraocular gas can also decrease scleral rigidity and alter the measurement of IOP. Goldmann tonometry, which produces very little volume displacement, is accurate compared with a mercury manometer inserted into eye bank eyes.⁷⁰ Schiøtz tonometry and pneumotonometry, however, which both use large-volume displacement, will underestimate the actual IOP in gas-filled eyes by 79% and 25%, respectively.⁷⁰ Even the Tono-Pen may underestimate IOP at levels above 30 mm Hg.⁷¹

PEARL... The Schiøtz tonometer, pneumotonometer, and Tono-Pen can all underestimate IOP in eyes with intraocular gas. Goldmann tonometry, which produces very little volume displacement, provides the most accurate IOP measurement in these eyes.

Although many surgeons do not routinely prescribe aqueous suppressants to prevent elevated IOP after vitrectomy, they may be appropriate for patients with pre-existing glaucoma who have optic nerve damage and decreased aqueous outflow.^{72,73} In eyes with healthy optic nerves, IOPs of 40 mm Hg or less are usually well tolerated and are adequately treated with topical or oral aqueous suppressants. However, higher pressures, as determined by Goldmann tonometry, usually require a paracentesis and removal of aqueous. Patients with expanding gas concentrations instilled following a vitrectomy and high IOPs may need a gas/fluid or gas/air exchange. These patients require immediate attention because they can develop severe, permanent loss of vision.

SILICONE OIL

Silicone oil, used for postoperative tamponade after repair of complex retinal detachments, frequently produces elevated postoperative IOP.⁷⁴ Mechanisms by which silicone oil can cause glaucoma include open-

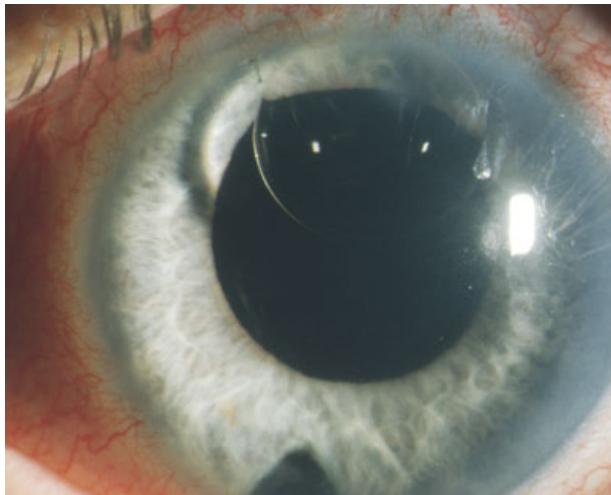
angle mechanisms and pupillary block, which can present either with an open angle and filling of the anterior chamber with oil, or a more typical collapse of the anterior chamber, usually from an overfilling of the posterior segment with oil.

Chronic IOP elevation with an open angle unobstructed by oil occurs in approximately 10% of patients that receive silicone oil.^{74,75} The mechanism probably results from trabecular meshwork dysfunction and infiltration with silicone oil bubbles, pigmented cells, and macrophages (Fig. 27–4A).^{76,77} This is supported by the increased incidence of glaucoma in aphakic compared with phakic patients, and the decrease in silicone oil emulsification with highly purified silicone oil, from which low-molecular-weight contaminants have been removed. However, even with highly purified silicone oil, a life table analysis has shown that only 30% of anterior chambers were gonioscopically free of emulsified oil by 3 years after surgery.⁷⁸

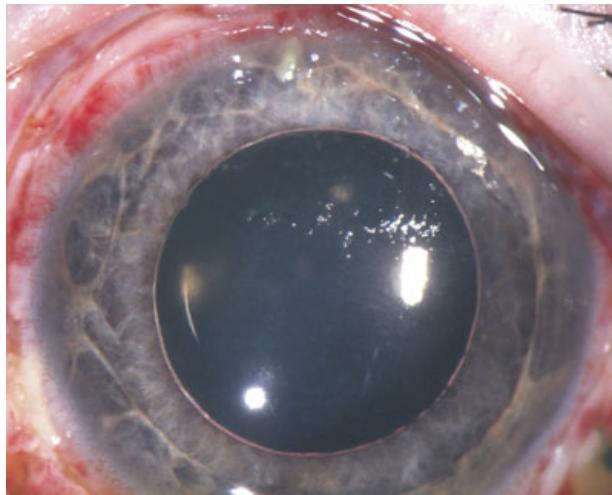
The best management of glaucoma from silicone oil emulsification is to prevent it by removing the oil 3 to 6 months after surgery, if possible. Patients may respond to removal of silicone oil even after glaucoma has developed. However, elevated IOP often persists, probably secondary to chronic changes in the meshwork due to inflammation in these diseased eyes. Although many eyes respond to medical glaucoma therapy, some will require adjunctive procedures, including endocyclophotocoagulation and aqueous shunts. Filtration surgery is often not possible due to conjunctival scarring from the prior retinal surgery. The surgeon should also remember that silicone oil removal is itself not without complications, and includes an approximately 20% risk of recurring retinal detachment.

Pupillary block caused by silicone oil is unique in that it does not often lead to a flat anterior chamber. In fact, failure to create an inferior peripheral iridectomy, or closure of the iridectomy, in aphakic and occasionally pseudophakic patients, may allow the oil to block the pupil and prevent aqueous from entering the anterior chamber. This leads to accumulation of aqueous in the posterior segment, which then forces the silicone oil into the anterior chamber. As anterior chamber aqueous leaves the eye via the trabecular meshwork, it becomes completely replaced by oil.

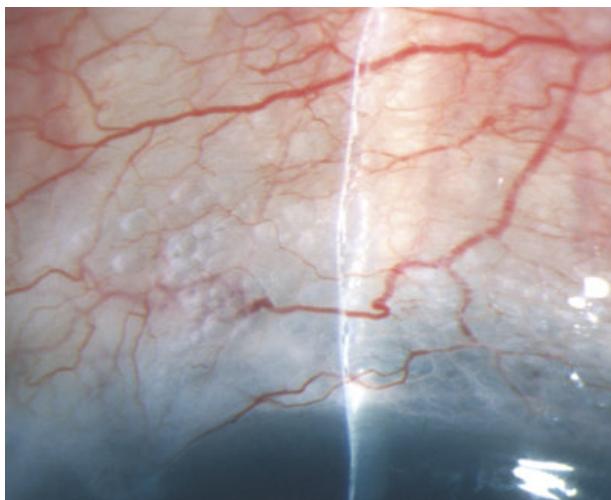
The subsequent total obstruction of the meshwork by oil leads to a severe and acute rise in the IOP. Because the anterior chamber is filled with silicone oil, these eyes may not have cells or flare, or even corneal edema, in spite of very high pressures (Fig. 27–4B). However, these eyes will often demonstrate an abnormally deep anterior chamber and a dilated pupil. A characteristic glistening of the slit beam from the iris and angle structures generally indicates the presence of silicone oil in the



A



B



C

FIGURE 27-4 Glaucoma and silicone oil. (A) Suspended bubble of oil in the anterior chamber, despite an inferior peripheral iridectomy to allow forward movement of aqueous humor. Intraocular pressure is elevated, probably from cumulative trabecular meshwork damage. (B) Pupillary block glaucoma from silicone oil presents with an apparently open angle and an unusually clear cornea and anterior chamber. Bright, pupillary border reflex indicates a reflective interface between the oil and iris. (C) Silicone oil in an eye with a trabeculectomy demonstrates subconjunctival bubbles of oil in the filtering bleb.

anterior chamber. This reflection, produced by the oil-tissue interface, is best observed with coaxial illumination, although varying the angle of the slit beam may occasionally be necessary.

SPECIAL CONSIDERATION

A clear cornea and a deep and quiet anterior chamber in spite of marked IOP elevation following silicone oil should alert the surgeon to the possibility of pupillary block and an oil-filled anterior chamber.

If an inferior peripheral iridectomy was created at the time of surgery, it should be carefully inspected. If it is not patent, or if not performed at the time of surgery, an iridotomy should be created with the YAG laser. These iri-

dotomies should be relatively large because they tend to close, due to their inferior location and cellular proliferation along the anterior and posterior iris surfaces. A successful iridotomy often produces immediate migration of aqueous into the anterior chamber, with posterior migration of the silicone oil.

If IOP is high despite a patent iridectomy, the surgeon should consider the possibility of silicone oil overfill in the early postoperative period. Alternatively, a posterior space-occupying lesion, such as a suprachoroidal hemorrhage or tractional retinal detachment, can decrease the volume of the posterior segment and force the silicone oil anteriorly, especially in aphakic patients. Management of these conditions involves treating the underlying cause or removing the oil. In spite of these measures, elevated pressure may persist due to permanent trabecular damage and may require aqueous shunt placement (following removal of the oil), or cyclodestruction, if the silicone oil cannot be safely removed (Fig. 27-4C).

PERFLUOROCARBON LIQUIDS

Perfluorocarbon liquids, such as perfluoroperhydrophenanthrene and perfluorodecalin, are heavier than water agents that are used in the hydrokinetic manipulation of the retina during vitrectomy. When used during vitrectomy, they do not appear to increase the rate of postoperative glaucoma, as long as they are completely removed at the end of surgery.⁷⁹

When it occurs, glaucoma from perfluorocarbon liquids appears to result from one of two mechanisms. The first of these is angle closure from overfilling the posterior segment with the perfluorocarbons, or if a large volume of perfluorocarbon is left in the anterior segment. The second mechanism occurs in patients with silicone oil. Here, small droplets of perfluorocarbon, which settle inferiorly in the anterior segment, occlude the inferior surgical iridectomy, leading to silicone oil-induced pupillary block, as described above. These patients are best managed by removing the perfluorocarbon liquid.^{80,81}

SCLERAL BUCKLING PROCEDURES

Mild shallowing of the anterior chamber is not uncommon following a scleral buckle for rhegmatogenous retinal detachment. However, some patients develop angle-closure glaucoma. Because this angle closure can occur in patients who are aphakic and possess surgical iridectomies, it does not appear to be due to pupillary block. Instead, the mechanism is thought to be edema of the ciliary body and/or supraciliary effusion, with anterior rotation of the ciliary body. In one ultrasound biomicroscope study, 80% of patients following scleral buckling surgery demonstrated increased supraciliary fluid and ciliary body thickness. Although 20% had complete closure of the angle over one to three quadrants, none developed symptoms of angle-closure glaucoma.⁸² Treatment includes aqueous suppressants, and cycloplegia with atropine or scopolamine. Miotics should be avoided.

Open-angle glaucoma may also occur after scleral buckling procedures. This can happen in patients with pre-existing primary open-angle glaucoma or Schwartz's syndrome, and they may require aqueous suppressants during the perioperative period. Some eyes require intraocular gases along with this surgery, and this possibility should also be considered in patients with glaucoma following a scleral buckle.

PANRETINAL PHOTOCOAGULATION

Although PRP decreases the overall incidence of glaucoma by preventing the development of neovascular glaucoma,⁸³ patients can develop increased IOP imme-

diate after treatment.⁸⁴ These patients usually begin with an open angle, but anterior chamber depth often decreases after PRP, leading to angle closure.⁸⁵ Probable mechanisms include swelling and anterior rotation of the ciliary body, or displacement of the lens–iris diaphragm induced by accumulation of supraciliary fluid.

Performing PRP in two or more settings will usually avert this complication. If it does occur, the treatment is cycloplegia to deepen the anterior chamber, topical glucocorticoids, and pressure-lowering agents, such as carbonic anhydrase inhibitors, alpha₂-agonists, and beta-blockers, as needed.

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GLAUCOMA AFTER ANTERIOR SEGMENT SURGERY

Martin B. Wax, M.D., and James Umlas, M.D.

Although normal individuals usually tolerate transient rises in intraocular pressure (IOP), postoperative pressure elevation in eyes with preexisting glaucoma can lead to further visual field loss, including loss of fixation.^{1–3} Because of this, the anterior segment surgeon must always strive to prevent postoperative ocular hypertension and manage it aggressively when it occurs.

The causes of elevated IOP following cataract surgery are numerous, and their relative frequency has changed with evolving surgical techniques. The gradual transition to extracapsular techniques and modern posterior chamber intraocular lenses (IOLs) have diminished the occurrence of enzymatic glaucomas and the uveitis-glaucoma-hyphema (UGH) syndrome.⁴ However, capsular block syndromes, epithelial ingrowth, pigment dispersion, retained viscoelastics, and post-neodymium:yttrium-aluminum-garnet (Nd:YAG) capsulotomy IOP spikes can still produce a variety of postoperative pressure problems.⁴ Table 28–1 lists the causes of glaucoma following cataract surgery. Open- and closed-angle mechanisms are discussed in the following two sections. However, several mechanisms, including intraocular hemorrhage, ghost cell glaucoma, epithelial and fibrous ingrowth, and malignant glaucoma can occur with all forms of anterior segment surgery and are discussed in separate sections at the end of this chapter.

Patients undergoing penetrating keratoplasty (PKP) can also develop postoperative pressure rises through mechanisms that are unique to this type of surgery. Other specific causes, such as steroid-induced and uveitic glaucoma and glaucoma following retinal surgery, are discussed in Chapters 18, 26, and 27, respectively.

OPEN-ANGLE GLAUCOMA AFTER CATARACT SURGERY

Fewer than 10% of glaucoma patients experience increased difficulty in long-term IOP control after cataract surgery.⁵ Although some studies report that cataract extraction produces a long-term IOP reduction, others do not.^{1,6–9} The occurrence of this complication depends on the status of a patient's preexisting glaucoma, as well as on the surgical techniques employed.

TABLE 28–1 CAUSES OF GLAUCOMA FOLLOWING CATARACT SURGERY

<i>Open Angle</i>	<i>Closed Angle</i>
Preexisting glaucoma	Pupillary block
Obstruction from viscoelastics, red blood cells, and debris	Capsular block syndrome
Trabecular meshwork deformation	Neovascular glaucoma
Enzymatic glaucoma	Epithelial and fibrous ingrowth*
Cyclodialysis cleft closure	Malignant glaucoma*
Intraocular hemorrhage and ghost cell glaucoma*	
Retained nuclear fragments	
Lens particle glaucoma	
Uveitis-glaucoma-hyphema syndrome	
Pigment dispersion	

* May occur with any type of anterior segment surgery.

CONTROVERSY

The effect of cataract extraction on chronic glaucoma control varies, depending on the status of preexisting glaucoma and the surgical techniques employed.

BACKGROUND

Although acute IOP spikes occur in fewer than 50% of nonglaucomatous patients,¹⁰ the incidence of continued IOP elevations after several months is probably lower than 5%.^{1,10,11} However, an early IOP rise that is sustained during the first several months postoperatively may forecast long-term difficulty with IOP control.¹²

Seventy to 80% of primary open-angle glaucoma (POAG) patients may have elevated IOP (greater than 21 mm Hg, or a 10 mm Hg rise above baseline) 1 day after extracapsular cataract extraction (ECCE).^{13,14} Small incision techniques may cause fewer acute IOP spikes. However, short-term IOP elevation in the first postoperative week remains a common problem,^{9,15–18} and elevated pressures can persist for months after surgery. Some studies suggest that prior glaucoma surgery reduces the risk of postoperative pressure spikes.¹⁹ However, patients with prior laser trabeculoplasty or glaucoma filtering surgery can still develop medically uncontrollable IOP after cataract surgery.²⁰

SPECIAL CONSIDERATION

An early IOP rise that is sustained in the first several months postoperatively may be associated with long-term difficulty in IOP control.

Posterior chamber IOLs or semiflexible, open-loop anterior chamber IOLs do not seem to adversely affect long-term IOP control in either glaucomatous or nonglaucomatous eyes.^{1,21} Silicone and acrylic foldable posterior chamber IOLs appear to have similar long-term IOP results.²²

PATOPHYSIOLOGY

Reduced outflow facility likely predisposes the glaucomatous eye to transient IOP elevation following cataract surgery. Additional impairment to outflow probably results from trabecular obstruction from viscoelastic agents and debris in the anterior chamber.^{23,24} Other factors include mechanical deformation of the trabecular meshwork by suturing of conventional, 10 to 11 mm superior corneoscleral wounds. In addition, protein, iris pigment, red blood cells, and lens particles may temporarily obstruct the remaining functional meshwork and produce elevated IOP. Specific causes are discussed in the following text.

COMPLICATIONS

Phacoemulsification and implantation of posterior chamber lenses in eyes with preexisting glaucoma are now widely practiced and are generally safe. However, even transient elevations of IOP may cause further glaucomatous field loss or precipitate anterior ischemic optic neuropathy or a major vascular occlusion.

Eyes with severe glaucoma damage are likely to develop wide fluctuations in IOP. Both intracapsular and extracapsular cataract surgery can produce further visual field loss in approximately 9% of such eyes in the early postoperative period.^{1,25}

Hayreh has suggested that the transient pressure rise after cataract surgery may cause hypoperfusion of the optic nerve head and lead to anterior ischemic optic neuropathy.²⁶ Patients with a history of this complication in one eye, and eyes that have a cupless and small optic disk are at higher risk for this complication. These eyes require careful IOP monitoring after cataract surgery.

PITFALL... In eyes with a cupless and small optic nerve head (“the disc at risk”), IOP should be monitored closely to detect potential ischemic damage. This may appear initially as papillitis and then progress to anterior ischemic optic neuropathy.

Acute glaucoma has also been associated with central vein occlusion. This probably results from increased IOP impairing venous drainage, particularly when combined with preexisting atherosclerosis and an extensively cupped, rigid optic nerve head.

MANAGEMENT

Prophylaxis

Prophylaxis remains the most effective method of avoiding a pressure rise after cataract surgery. Theoretically, small-incision surgery and clear corneal incisions should reduce mechanical disturbance of the trabecular meshwork. Removal of residual blood, pigment, or lens material from the anterior chamber at the time of surgery is desirable. In addition, removing or diluting sodium hyaluronate may partially reverse its effects on postoperative IOP.²⁷ Other viscoelastics, such as chondroitin sulfate, may have a more temporary effect on IOP than hyaluronic acid, although the evidence for this is contradictory.²⁸

Studies provide mixed results on the value of using prophylactic preoperative medications to avert IOP elevation after cataract surgery. Intracameral carbachol 0.01%, instilled at the end of surgery, is more effective during the first postoperative day than either balanced salt solution or acetylcholine.^{29,30} Pilocarpine gel 4% appeared to be more effective than pilocarpine 4% solution, timolol 0.5% solution, or placebo.^{31,32}

In the past, nonspecific beta-adrenergic antagonists were widely advocated for control of postoperative IOP,^{33,34} although not all studies support this idea.³⁵ The efficacy of perioperative systemic carbonic anhydrase inhibitors (CAIs) is similarly mixed.^{36,17,37,38} Topical dorzolamide and systemic CAI appear to have similar efficacy.³⁹

Apraclonidine 0.5 to 1.0%, given in conjunction with cataract or combined cataract and trabeculectomy surgery, may also reduce the incidence of postoperative elevation.^{38,40,41} Although the optimal time to administer the drug is unclear, many surgeons favor a single dose 1 hour before surgery.

Although prostaglandin analogs may help prevent postoperative IOP rise in selected patients, many surgeons do not use them postoperatively due to the possible association with uveitis and cystoid macular edema. Nonsteroidal antiinflammatory agents have little effect on IOP elevation after cataract extraction.⁴²

Cataract extraction alone in patients with POAG and good preoperative IOP control can effectively lower postoperative IOP.^{16,43} However, cataract extraction combined with filtration surgery typically results in fewer IOP spikes, better overall IOP control with fewer antiglaucoma medications, and similar visual outcomes.^{13,44,45} The decision of which procedure to perform is fully discussed in Chapter 44.

When performed with a trabeculectomy, phacoemulsification may provide slightly better overall IOP control than ECCE, with faster visual rehabilitation and fewer complications.^{46–52} Although some studies indicate similar success for combined phacotrabeculectomy versus trabeculectomy alone,^{53,54} other data suggest that patients undergoing trabeculectomy alone will achieve better long-term IOP control.⁵⁵

CONTROVERSY

Although some studies indicate similar success for combined phacotrabeculectomy versus trabeculectomy alone, others suggest that trabeculectomy alone may provide better IOP control.

It appears that the one-site and two-site surgical approaches to combined phacotrabeculectomy can achieve similar IOP control. However, patients receiving single-site surgery may need more postoperative antiglaucoma medication.^{56,57} The choice of a limbus-versus fornix-based conjunctival flap does not appear to affect long-term pressure control.^{58,59}

Antimetabolites, used in conjunction with combined phacotrabeculectomy, may facilitate long-term IOP control.^{60,61} However, some investigators believe their use should be reserved only for cases with high risk for primary failure.^{62,63}

In patients with a functioning filtering bleb, phacoemulsification through a clear corneal incision does not

appear to adversely effect long-term IOP control.⁶⁴ Although less common than with ECCE,⁶⁵ IOP can still rise significantly after clear cornea phacoemulsification.⁶⁶ Risk factors for worsening trabeculectomy function following cataract extraction include patient age under 50 years, preoperative IOP of greater than 10 mm Hg, intraoperative iris manipulation, and early postoperative IOP greater than 25 mm Hg.⁶⁷

Treatment of Elevated Intraocular Pressure

Treatment of elevated IOP, when it occurs, begins with topical and/or systemic aqueous suppressants. Oral or intravenous hyperosmotic agents are reserved for cases with severe or unresponsive elevations of IOP. Unless there is a hyphema or other obvious abnormality, medical treatment should be continued for 48 to 72 hours to allow spontaneous improvement.

Cases with severe IOP elevation or extensive glaucomatous optic nerve damage may require immediate IOP lowering. This can be accomplished at the slit-lamp by aspirating aqueous humor through the paracentesis, followed by close monitoring because IOP may rise again within minutes to hours.

PEARL... Aspiration of aqueous via a preplaced paracentesis incision offers rapid relief from an excessive postoperative intraocular pressure rise after cataract surgery.

Some patients with persistent pressure elevations following cataract surgery require laser treatment for specific glaucoma conditions. These include a peripheral iridotomy for pupillary block, laser trabeculoplasty for open-angle glaucoma, Nd:YAG anterior vitreolysis for malignant glaucoma, and panretinal photocoagulation or goniophotocoagulation for neovascular glaucoma. Refractory cases of sustained, elevated IOP may require filtering surgery, an aqueous shunt, or cyclophotocoagulation.

SPECIFIC CAUSES OF OPEN-ANGLE GLAUCOMA AFTER CATARACT SURGERY

Enzymatic (Alpha-chymotrypsin) Glaucoma

With the virtual disappearance of intracapsular cataract extraction, this entity is now largely historical. Glaucoma results from obstruction of the trabecular meshwork by zonular fragments created by alpha-chymotrypsin-induced zonulolysis.⁶⁸ The anterior chamber angle is open, and the IOP rise typically occurs several days after surgery and lasts days to weeks. This effect is less likely to occur with a smaller amount of a dilute 1:10,000 enzyme dilution (versus the standard 1:5,000 solution), followed by

careful anterior chamber irrigation. Prophylactic aqueous suppression may be helpful, and medical therapy usually controls postoperative IOP spikes.⁶⁹

Cyclodialysis Cleft Closure

A cyclodialysis cleft, caused by disinsertion of the scleral spur from the ciliary body, rarely occurs after cataract surgery. This allows anterior chamber fluid to escape into the suprachoroidal space and produces hypotony. This should be suspected in cases of persistent postoperative hypotony in which there is no wound leak present. Larger clefts can sometimes be identified by gonioscopy.

Sudden spontaneous or iatrogenic closure of cyclodialysis clefts can result in acute IOP spikes.⁷⁰ These are typically transient but can persist. Initial management usually consists of aqueous suppressants.⁴

Retained Nuclear Fragments After Cataract Surgery

Loss of nuclear fragments into the vitreous has become more common as more surgeons make the transition to phacoemulsification. Almost half of these patients develop elevated IOP.^{71,72} Other associated causes of elevated IOP include persistent uveitis, retinal detachment, and vitreous hemorrhage.

This form of glaucoma often resists medical treatment, especially if substantial portions of lens nuclear material are present. Anterior segment surgeons should resist the temptation to retrieve lens fragments located deep in the posterior segment. These cases are best treated by vitrectomy and lens fragment removal by a vitreoretinal surgeon. Early intervention appears to provide a better and more rapid visual acuity return but does not seem to affect the incidence of glaucoma.^{71,72}

Lens Particle Glaucoma

Lens particle glaucoma results when macrophages containing lens particles or inflammatory cells obstruct the trabecular meshwork.⁷³ In contrast to phacolytic glaucoma, the lens capsule is not intact, and high-molecular-weight proteins are absent. This typically occurs shortly after cataract surgery or penetrating trauma, but can occur remotely, even after Nd:YAG capsulotomy with release of previously sequestered lens material. This form of lens-induced glaucoma is discussed in Chapter 25.

Uveitis-Glaucoma-Hyphema Syndrome and Pigment Dispersion

IOL implants can cause chronic uveitis, either through improper positioning or from excessive movement of the implant (Fig. 28-1A,B). This complication was much more common with early, closed-loop, rigid anterior chamber lenses,^{74,75} especially if their fixation was insecure or if their haptics rested near preexisting synechiae or eroded into the angle structures. The inflammation occasionally leads to further trabecular damage, progressive anterior and posterior synechia formation, sequestration of the pupil, and secondary angle-closure glaucoma.

Some cases develop neovascularization adjacent to the haptics, causing a combination of uveitis, glaucoma, and hyphema (the UGH syndrome). Although removal of the IOL is necessary in some cases, this is invariably traumatic and is indicated only if more conservative therapy fails.⁷⁶

An open-angle glaucoma that resembles pigment dispersion occasionally follows implantation of a posterior chamber IOL. These cases are typically unilateral and are associated with peripheral iris transillumination defects and increasing pigmentation of the trabecular meshwork.⁷⁷ The transillumination defects, localized in the area of the IOL haptics, indicate progressive posterior pigment

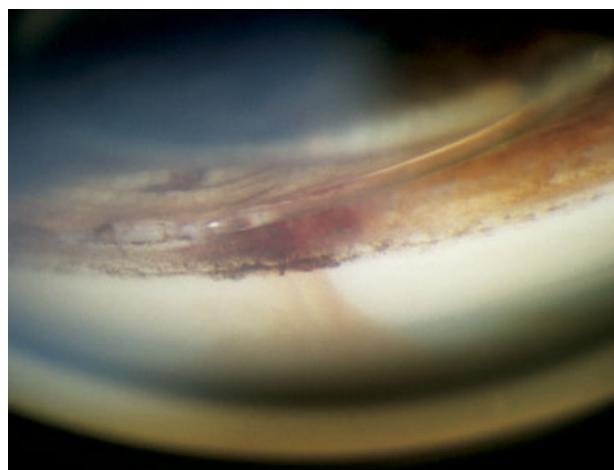


FIGURE 28-1 (A) Uveitis-glaucoma-hyphema from a rigid anterior chamber intraocular lens. (B) Bleeding typically results from erosion of IOL haptic into the iris root or ciliary body, as shown by gonioscopy (A) or by direct observation at the slit lamp.

shedding. This condition is more likely with sulcus-fixated IOLs and usually evolves in the first few months after surgery. These cases respond well to medical therapy and may be self-limited. Severe cases may require laser trabeculoplasty or trabeculectomy.

ANGLE-CLOSURE GLAUCOMA AFTER CATARACT EXTRACTION

Angle-closure glaucoma following cataract surgery can result either from pupillary block or from chronic angle closure due to several associated conditions. This section discusses the conditions that specifically relate to cataract surgery.

PUPILLARY BLOCK

IOLs, lens material, the lens capsule, vitreous, blood, fibrin, or intraocular gas injected at the time of surgery can all produce pupillary block glaucoma. This can occur in aphakia or pseudophakia, and can follow occlusion of an iridectomy (Fig. 28–2A,B). Generally, the anterior chamber appears flat or shallow, and the angle is closed gonioscopically. However, pupillary block from an anterior chamber IOL will produce a deep central chamber with peripheral iris bombé.

Established pupillary block is typically treated with aqueous suppressants and miotics, although it may respond to vigorous dilation and cycloplegia, which temporarily reduces IOP. If an iridectomy has been omitted or becomes obstructed, then a laser iridotomies is indicated. In some cases, an intact vitreous face can continue to occlude an iridectomy site, and laser disruption with the Nd:YAG laser is required posterior to the iridectomy. After resolution of the pupillary block, the surgeon should perform gonioscopy to rule out residual synechial angle closure.^{4,78}

CAPSULAR BLOCK SYNDROME

Capsular block syndrome is an unusual condition with distention of the capsular bag and anterior chamber shallowing.

following phacoemulsification with a posterior chamber lens implant.^{79–81} This typically follows an uncomplicated surgery, using continuous curvilinear capsulorhexis and viscoelastic. Within 1 day to several weeks, the anterior chamber appears to shallow, with marked distention of the posterior lens capsule and a large space with suspended cells between the posterior capsule and posterior chamber IOL. The anterior lens capsule rim is completely apposed to the peripheral anterior surface of the IOL, and a fibrotic sheen or “paste” appears on the anterior IOL surface. Unexpected myopic shifts are often observed, but elevated IOP is infrequent.

Proposed mechanisms generally postulate that retained viscoelastics or lens epithelial cells increase oncotic pressure behind the posterior chamber IOL (PCIOL), producing fluid accumulation within the bag. Although this condition usually resolves spontaneously, some cases will require Nd:YAG capsulotomy to decompress the capsular bag and allow the IOL to move posteriorly.^{79,80} This can be performed on the anterior capsule, peripheral to the IOL optic, or as a posterior capsulotomy.

NEOVASCULAR GLAUCOMA

Neovascular glaucoma (Chapter 21) can develop after cataract extraction and Nd:YAG capsulotomy, especially in diabetics with proliferative retinopathy. Presumably, this occurs because the compromised posterior capsule allows angiogenic factors from ischemic retina to gain access to the anterior chamber.^{82,83} Initial treatment consists of pan-retinal laser photoocoagulation or cryotherapy, and aqueous suppressants, cycloplegics, and topical corticosteroids.

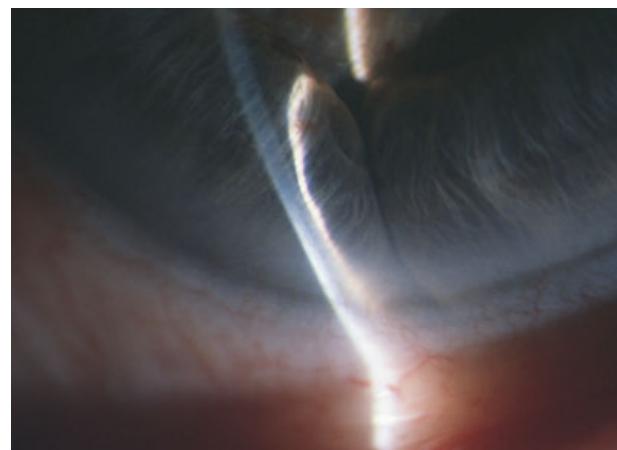
GLAUCOMA AFTER PENETRATING KERATOPLASTY

BACKGROUND

Glucoma following penetrating keratoplasty (PKP) occurs in 10 to 35% of cases.^{84–87} Certain groups of



FIGURE 28-2 Pupillary block from anterior chamber intraocular lens is seen with characteristic iris bombé by direct observation (A) or with a slit beam (B), which shows the bulging iris pushed against the posterior cornea.



B

patients have substantially higher risk for developing glaucoma after keratoplasty. They can be distinguished by various preoperative and intraoperative factors.^{85,86,88}

Preoperative factors include preexisting glaucoma, aphakia,^{84,85,89} pseudophakic bullous keratopathy,⁹⁰ history of trauma,⁹¹ and anterior segment dysgenesis.^{84,87} In eyes with preexisting glaucoma, the chance of exacerbation following PKP increases with the number of preoperative glaucoma medications.⁸⁶ In aphakic eyes, the lack of posterior zonular tension on the trabecular meshwork may further decrease aqueous outflow.⁹² The glaucoma associated with pseudophakic bullous keratopathy is often related to closed-loop or pupil-supported IOLs.⁹³

Intraoperative factors that appear to influence the incidence of glaucoma after PKP include graft size, the use of viscoelastics, and management of peripheral anterior synechiae (PAS). Using donor corneal grafts that are larger than the host beds results in greater outflow facility and lower postoperative IOP after PKP.⁹⁴ However, the effect may only be short term and appears to be greater in aphakic than phakic eyes.^{95,96} Viscoelastic agents do appear to cause early, self-limited IOP elevation after PKP. Patients with PAS prior to PKP or those at risk for development of synechial angle closure may benefit from iridoplasty at the time of surgery.⁹⁷ There is no consensus regarding the relationship of concurrent anterior vitrectomy, IOL removal, repeat grafting, triple procedure (cataract extraction, IOL placement, and PKP), anterior segment reconstruction, or transscleral sutured IOL placement to the development of post-keratoplasty glaucoma.

A history of pre- or post-PKP glaucoma has a negative prognostic effect on corneal graft survival.⁹⁸ In addition, a pigment dispersion syndrome has been reported after PKP with posterior chamber IOL placement and must be considered in the differential diagnosis of graft rejection.⁹⁹

PATHOGENESIS

Potential mechanisms of glaucoma following PKP include steroid-induced glaucoma, pupillary block, and extensive PAS formation.¹⁰⁰ In some cases, choroidal effusion and iris swelling with forward rotation of the ciliary body produce insidious angle closure.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The primary diagnostic difficulty following PKP rests on the difficulty of accurately measuring IOP using standard tonometric techniques. Significant astigmatism and corneal edema may render Goldmann applanation readings inaccurate, whereas Schiøtz readings may be inaccurate in high myopes and infants with reduced scleral rigidity. MacKay-Marg and pneumatic tonometers give more accurate readings, whereas the Tonopen appears to underestimate highly elevated IOPs.⁸⁸

Accurate IOP measurement becomes particularly important in patients with epithelial edema of the graft, which could be due to marked IOP elevation versus possible graft failure or rejection. A careful contact lens exam may improve visualization of the optic disc to determine the degree of glaucomatous cupping.

MANAGEMENT

Medical treatment initially involves topical aqueous humor suppressants used alone or in combination. Cycloplegics are used as needed, and most surgeons generally avoid miotics. Hyperosmotics may be necessary in short-term situations where other medical therapy has been ineffective. Nonpreserved timolol, levobunolol (with low benzalkonium chloride concentration) or oral CAIs can be used in cases with corneal epithelial toxicity.⁸⁸

Laser therapy can include, rarely, argon laser trabeculoplasty (ALT) for open-angle glaucoma following PKP¹⁰¹ and Nd:YAG peripheral iridotomy for pupillary block. Relatively new synechial closure (i.e., less than 1 year old) may respond to gonioplasty or goniosynechialysis.⁸⁸ Nd:YAG and diode cyclophotocoagulation can effectively lower IOP. However, multiple treatments are often necessary, and hypotony, graft failure, and deterioration of vision may occur (Chapter 42).¹⁰²⁻¹⁰⁴

Filtration surgery in eyes with intractable glaucoma can effectively control IOP, but usually requires antimetabolites.¹⁰⁵ Although aqueous shunts generally provide good IOP control, several studies report a high incidence of corneal graft failure following these devices.¹⁰⁶⁻¹⁰⁸

Combined PKP and trabeculectomy is associated with a good graft survival rate, but there may be some increased risk for early failure of IOP control.¹⁰⁹⁻¹¹¹ Many clinicians strongly advocate controlling glaucoma prior to PKP, using any of the methods already described.

PITFALL... Many clinicians strongly advocate that glaucoma control should precede penetrating keratoplasty. This may include seton placement via the pars plana in pseudophakic or aphakic patients, following a vitrectomy.

GLAUCOMA FOLLOWING ANTERIOR SEGMENT LASER SURGERY

ALT, argon and Nd:YAG peripheral iridotomy, and Nd:YAG posterior capsulotomy can all elevate IOP.^{112,113} Ocular hypertension typically occurs within 2 hours after the procedure and is short in duration, but occasionally can be chronic,¹¹⁴ or even remote.¹¹⁵ An acute pressure rise after ALT may be associated with visual field loss.¹¹⁶ Post-laser IOP spikes are typically more common in

aphakes than pseudophakes.^{112,113} High myopia and preexisting glaucoma may be risk factors for this complication following posterior capsulotomy.

Most reports indicate that total laser energy and the number of pulses are not related to the level of IOP rise following posterior capsulotomy.^{112,114,117,118} However, the incidence and degree of IOP rise after ALT is greater in eyes undergoing 360 versus 180 degrees of treatment.^{116,119} YAG and argon peripheral iridotomies appear to have an equal incidence of post-laser IOP spikes.¹²⁰

IOP elevation after posterior capsulotomy probably results from obstruction of the trabecular meshwork by capsular and lens debris. Obstruction following iridotomy is due to iris pigment and debris. All of these procedures may produce inflammation.^{117,121} Although unusual, ALT can lead to uveitis, PAS formation or trabeculitis, and a delayed elevation of IOP.^{122,123}

Although beta-adrenergic antagonists and CAIs have been used to prevent IOP spikes following anterior segment laser procedures, 0.5 and 1.0% apraclonidine are particularly effective.^{124–127} Pressure spikes generally occur 1 to 2 hours after laser.^{112,113,124}

PEARL... The intraocular pressure should always be checked 1 hour after anterior segment laser procedures.

For patients with sustained elevation of IOP after anterior segment laser, more unusual causes, such as steroid-induced glaucoma, PAS, trabeculitis, and uveitis must be ruled out. Typically, antiglaucoma medicines are sufficient to treat the IOP elevation, although some cases require filtration or aqueous shunt surgery.

POSTOPERATIVE HYPHEMA

Postoperative hyphemas generally result from vascularized wound incisions or from intraoperative iris trauma. IOP elevation occurs from trabecular obstruction by red cells, fibrin, and inflammatory cells. Although the angle is usually open, persistent inflammation can induce secondary angle closure.

Elevated IOP should be treated with aqueous suppressants and topical corticosteroids while avoiding miotics, aspirin, warfarin, and nonsteroidal anti-inflammatory drugs. Patients with sickle cell disease or trait should not receive CAIs. A markedly elevated IOP (greater than 50 mm HG for 5 days or more, or greater than 35 mm HG for a week or more), corneal bloodstaining, or a total hyphema that persists for several days all warrant surgical intervention. Patients with compromised optic nerves may need surgical removal of blood for less severe pressure elevations.

Occasionally, a hyphema occurs long after the original surgery. This typically results from neovascularization bridging a wound or from repeated contact of an IOL on the iris or ciliary sulcus tissue. Eyes that do not respond to conservative medical management may benefit from argon laser goniophotocoagulation of the responsible vessels, if visible. For repeated IOL trauma, the lens may have to be rotated, replaced, or removed.⁴

HOST CELL GLAUCOMA

Ghost cell glaucoma (Chapter 24) generally occurs several weeks after vitreous hemorrhage. The vitreous acts as a reservoir for erythrocytes, which lose hemoglobin and degenerate after several weeks, leaving behind khaki-colored, rigid red blood cell membranes. They may be seen circulating in the anterior chamber, coating the corneal endothelium, layered in a hypopyon, or lining the trabecular meshwork. The angle is open and pressure is elevated, due to obstruction of the trabecular meshwork by these rigid cells. Antiglaucoma medications may control IOP until the cells clear, but in many cases, the source of the cells must be removed. Although a simple anterior chamber washout may be successful, persistent IOP elevation requires a complete vitrectomy.^{4,128}

EPITHELIAL INGROWTH

BACKGROUND

The overall incidence of epithelial ingrowth appears to have decreased with the increased popularity of extracapsular and small incision phacoemulsification techniques. It now occurs in less than 0.1% of cataract surgeries,¹²⁹ although it can arise even after sutureless phacoemulsification.^{130,131} This condition can also follow any type of penetrating intraocular surgery or trauma.

PATHOPHYSIOLOGY

The predisposing factors for epithelial ingrowth include a history of trauma or complicated surgery with poor wound apposition and incarceration of tissue. Additional factors are postoperative hypotony, fistula or bleb formation, and chronic postoperative inflammation. Chronic anterior chamber inflammation, exposed uvea, PAS, or vitreous incarceration can all encourage epithelial proliferation.¹³²

Epithelial ingrowth can diminish aqueous outflow by covering the trabecular meshwork, and the meshwork itself may become secondarily necrotic and fill with circulating epithelial and inflammatory cells.¹³³ Chronic iridocyclitis may cause a trabeculitis and induce PAS. These obstruct the angle and provide a surface for proliferating epithelial cells.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Epithelial ingrowth can present in several ways. "Pearl tumors" are rare, cystlike structures implanted on the iris surface, remote from the site of the original wound. They consist of encapsulated stratified squamous keratinizing epithelium and rarely cause sequelae. If they become large or induce iridocyclitis, they generally can be excised, with good outcomes.¹³²

Epithelial cysts are gray or translucent, usually connected to the entrance wound and generally avascular. Sheetlike epithelial ingrowth typically manifests as a gray, often scalloped, posterior corneal membrane, with varying thickness and occasional overlying corneal edema (Fig. 28-3A–E). In both conditions, slit-lamp and gonioscopic examination may reveal incarceration of the vitreous, iris, or lens capsule in the wound. All of these can provide a scaffold for the epithelium to grow into

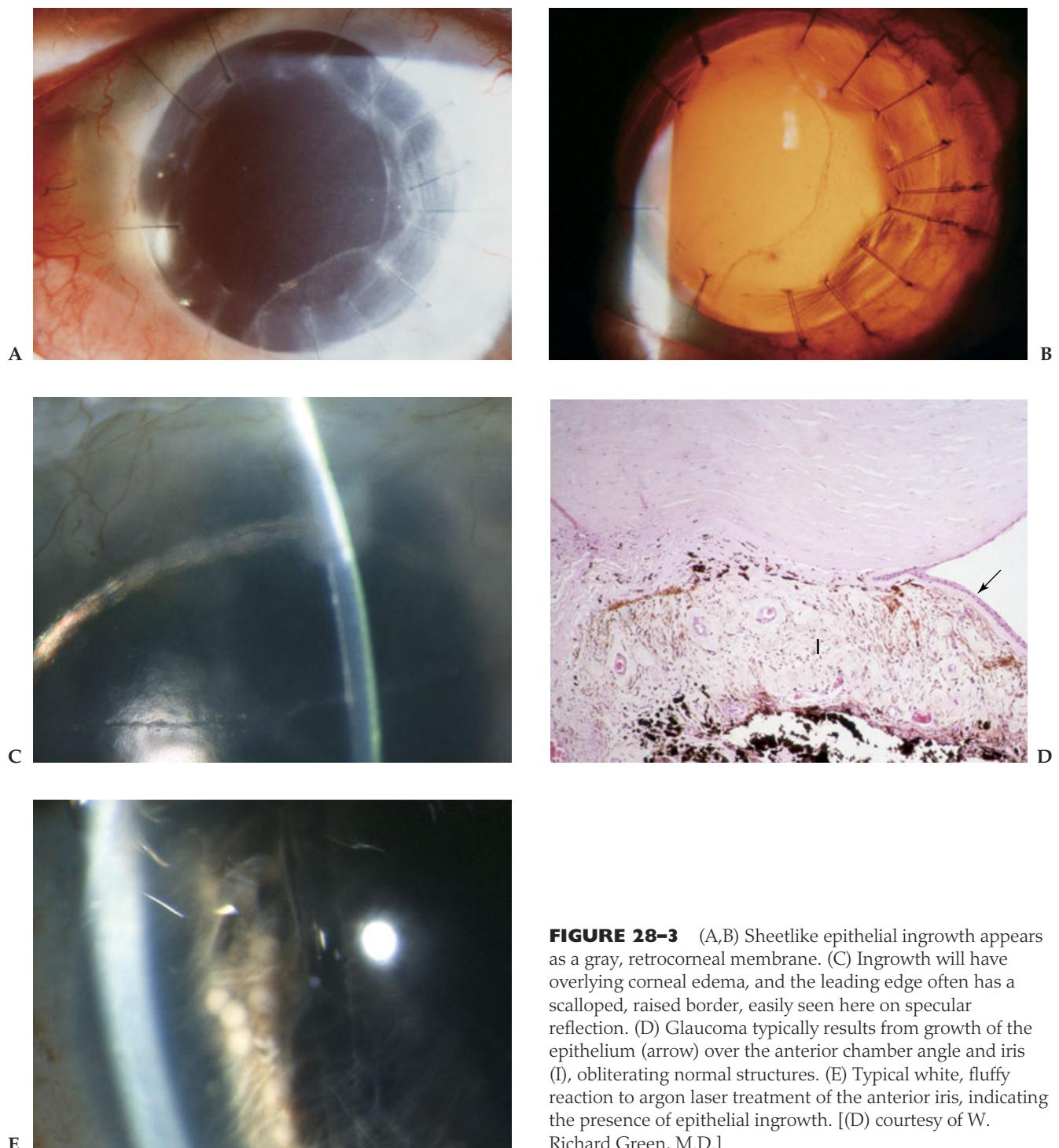


FIGURE 28-3 (A,B) Sheetlike epithelial ingrowth appears as a gray, retrocorneal membrane. (C) Ingrowth will have overlying corneal edema, and the leading edge often has a scalloped, raised border, easily seen here on specular reflection. (D) Glaucoma typically results from growth of the epithelium (arrow) over the anterior chamber angle and iris (I), obliterating normal structures. (E) Typical white, fluffy reaction to argon laser treatment of the anterior iris, indicating the presence of epithelial ingrowth. [(D) courtesy of W. Richard Green, M.D.]

TABLE 28-2 DIAGNOSIS OF EPITHELIAL INGROWTH

History	Trauma and/or complicated, multiple anterior segment surgeries Decreased visual acuity
Symptoms	Pain Injection Tearing
Signs	Anterior chamber cyst Gray, scalloped retrocorneal membrane Corneal edema Elevated intraocular pressure Distortion of anterior iris architecture Wound leak Wound incarceration (iris, lens material or capsule, vitreous) White reaction to iris laser Positive cytology from aqueous or vitreous

the eye. A sheetlike membrane may also cover angle structures, the iris surface, the IOL, the pupillary space, or the anterior vitreous face, as well as suture tracks and internal wound gaps.¹³²

The signs and symptoms of epithelial ingrowth may begin days to decades after the original surgery, although most cases present within the first year (Table 28-2).¹²⁹ Symptoms include decreased vision, pain, redness, and tearing. The most common signs are a retrocorneal membrane, glaucoma, corneal edema, and a positive Seidel test.

Other diagnostic methods to help identify epithelial ingrowth include argon laser to the iris surface, iris biopsy, anterior chamber curettage, or cytologic examination of an aqueous humor aspirate or vitrectomy.¹³² The simplest of these, argon laser photocoagulation, uses spots of laser (500 μm, 100 mW, and 0.1 seconds) to areas of suspected iris involvement. Whereas normal iris yields well-defined and atrophic lesions, iris covered with epithelium reacts with white, fluffy burns. This helps confirm the diagnosis and determines the extent of the ingrowth.¹³⁴ Specular microscopy may reveal a distinct border between epithelial and endothelial cells at the advancing edge of the ingrowth.

The differential diagnosis of epithelial ingrowth includes fibrous ingrowth, vitreocorneal adhesions, anterior shelved cataract incision, reduplication of Descemet's membrane, Descemet's tear, and corneal edema from intraoperative trauma. Fibrous ingrowth tends to be slow growing and is often more vascular in appearance. Vitreocorneal adhesions and shelved cataract incisions do not progress over time. Reduplicated Descemet's membrane will not produce a white lesion following argon laser photocoagulation.¹³²

MANAGEMENT

Treatment of epithelial ingrowth is often exceedingly difficult, and the results are frequently disappointing. The most accepted therapy is surgical extirpation.¹³⁴ This

involves identifying areas of iris involvement with the argon laser and closing any fistulae and removing incarcerated iris, vitreous, and lens tissue along with a generous anterior vitrectomy, repair of retinal breaks, and extensive cryotherapy to destroy the abnormal epithelial tissues. Complications include persistence of glaucoma, corneal edema, hypotony, and phthisis bulbi.¹³² Other proposed treatments include en bloc excision of involved tissues with grafting, endoresection of involved tissues with pars plana vitrectomy,¹³⁵ and intraocular antimetabolites.

Glaucoma management includes topical antiglaucoma agents and, if necessary, aqueous shunt implantation. Filtration surgery, even with antimetabolites, carries a high risk of failure due to invasion of the surgical site with epithelium, even involving the bleb itself.

FIBROUS INGROWTH

Although fibrous ingrowth progresses more slowly and is generally more benign than epithelial ingrowth, aggressive cases may produce similar sequelae. This rare condition appears to have predisposing conditions similar to those of epithelial ingrowth, although it may be more frequently associated with failed PKP.¹³⁶ It can present as a thick, vascularized membrane, which may be focal or can extend into the anterior chamber or even cover the entire endothelial surface of the corneal graft. Although the exact origin of proliferating fibroblastic cells is not clear, they may arise from subconjunctival connective tissue, stromal keratocytes, or metaplastic corneal endothelium. The differential diagnosis is similar to that of epithelial ingrowth but also includes corneal dystrophies and herpetic keratitis.¹³² When necessary, treatment is similar to that of epithelial ingrowth.

MALIGNANT GLAUCOMA (POSTERIOR AQUEOUS DIVERSION, CILIARY BLOCK)

Malignant glaucoma is an uncommon condition that can occur after any type of intraocular surgery or anterior segment laser surgery.^{137–140} Rarely, it can arise spontaneously.¹⁴¹ Management relies on proper recognition of the condition and understanding its unique mechanisms. Treatment includes cycloplegics and, if necessary, surgical removal of either the vitreous or other material responsible for aqueous diversion into the vitreous cavity.

PATHOPHYSIOLOGY

The fundamental mechanism of malignant glaucoma involves posterior misdirection of aqueous humor into, or behind, the vitreous (Fig. 28-4). This usually results from a block of aqueous flow into the anterior chamber at the junction of the ciliary processes, lens equator, and anterior

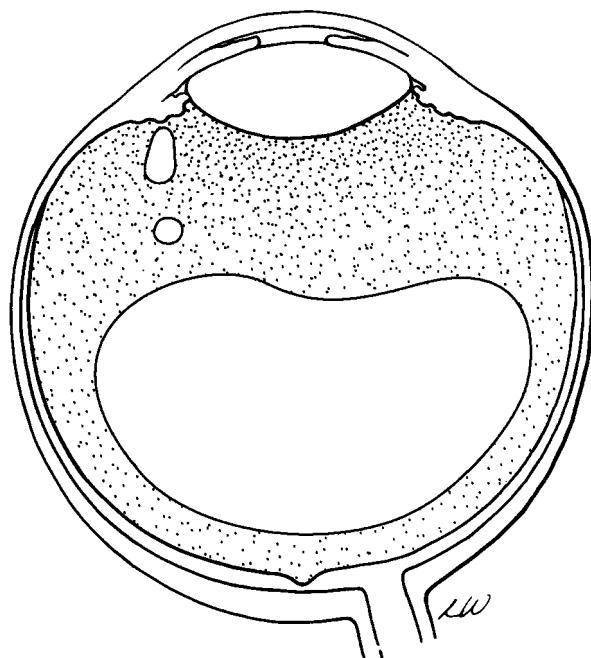


FIGURE 28-4 Aqueous misdirection involves diversion of aqueous humor posterior to the anterior hyaloid face (V). This causes shallowing of the anterior chamber with resultant angle closure.

hyaloid face.^{142,143} Increased fluid pressure in the vitreous cavity causes compaction of the anterior vitreous, leading to further decreased permeability and perpetuating a vicious cycle. The compressed vitreous is pushed forward and causes shallowing of the anterior chamber. This condition is more common in small, hyperopic eyes.

Malignant glaucoma begins in susceptible eyes following sudden decompression of the anterior chamber. This can occur during surgery or suture lysis, postoperatively from a wound leak, and, rarely, secondary to drugs that encourage anterior lens movement. Shallowing of the anterior chamber allows the peripheral anterior hyaloid to move into contact with the ciliary body and ciliary processes and initiates the movement of aqueous into the vitreous.¹⁴²

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Symptoms of malignant glaucoma range from decreased visual acuity from anterior lens movement to pain typical of highly elevated IOP (Table 28-3). Diagnostic signs involve marked axial shallowing of the anterior chamber in spite of a patent peripheral iridectomy or iridotomies (Fig. 28-5A–C). IOP is usually elevated above that expected for the clinical situation. This could consist of a relatively “normal” pressure in the presence of a functioning filtration bleb and an extremely shallow anterior chamber. Some cases will also have anteriorly rotated ciliary processes, or ciliary processes in close apposition to the lens equator.¹⁴³

The differential diagnosis of malignant glaucoma includes a persistent wound leak, pupillary block,

TABLE 28-3 DIAGNOSIS OF MALIGNANT GLAUCOMA (POSTERIOR AQUEOUS DIVERSION)

Symptoms	Decreased visual acuity Pain
Signs	Axial shallowing of anterior chamber Patent iridectomy “Elevated IOP” (in relation to the clinical situation) Ciliary process rotation/apposition with lens equator Absence of suprachoroidal fluid or blood Hyperopia in the fellow eye

choroidal detachments, iridovitreal block, and suprachoroidal hemorrhage. Pupillary block should be relieved by a patent iridectomy, which should be confirmed patent or reestablished if there is any uncertainty as to its patency.

Choroidal detachments, which are usually associated with hypotony, have rarely been associated with malignant glaucoma.¹⁴⁴ However, their presence as detected by funduscopic or ultrasound exam can establish with reasonable certainty that the patient does not have malignant glaucoma.

In iridovitreal block, which may be a variant of malignant glaucoma, the anterior hyaloid face is apposed to the posterior iris and iridectomy, preventing movement of aqueous and producing a shallowed anterior chamber, often with iris bombe. Posterior diversion of aqueous into the vitreous is probably not present, and vitrectomy is not necessary to relieve the condition. Slit-lamp exam usually reveals anterior hyaloid obstructing the iridectomy site. Laser iridotomy or Nd:YAG photodisruption of the posterior capsule or anterior hyaloid face is generally curative.^{143,145} A suprachoroidal hemorrhage typically presents with a painful, injected eye, and the hemorrhage is generally easily seen by ophthalmoscopic or ultrasound examination.

MANAGEMENT

Treatment of malignant glaucoma involves detection and closure of persistent wound leaks, aggressive cycloplegia, and treatment of glaucoma with aqueous suppressants and/or hyperosmotics. The cycloplegics are believed to tighten the zonules, which moves the lens–iris diaphragm posteriorly, resists the anterior pressure of the vitreous, and prevents posterior migration of aqueous.⁴ Miotics are contraindicated because they can produce the opposite effect.

If this treatment is successful, medications should be continued for weeks and then withdrawn gradually. In some patients, discontinuation of cycloplegics may result in a relapse, requiring indefinite therapy.

If the pressure remains uncontrolled after several days, or if a shallow chamber persists, then surgical measures are indicated to disrupt the anterior hyaloid surface and eliminate this barrier to anterior aqueous flow.¹⁴² Nd:YAG laser photodisruption of the peripheral anterior

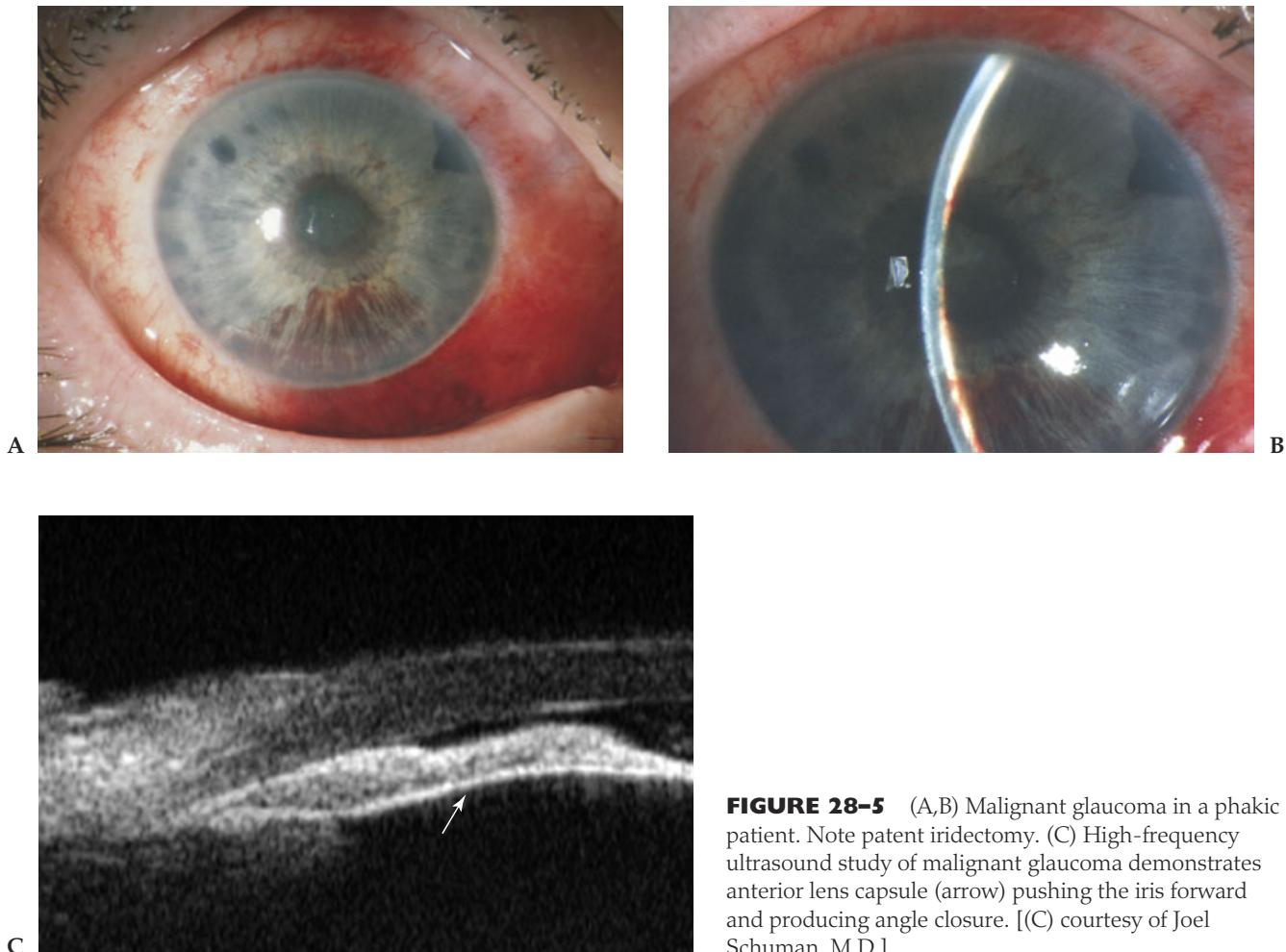


FIGURE 28-5 (A,B) Malignant glaucoma in a phakic patient. Note patent iridectomy. (C) High-frequency ultrasound study of malignant glaucoma demonstrates anterior lens capsule (arrow) pushing the iris forward and producing angle closure. [(C) courtesy of Joel Schuman, M.D.]

hyaloid face has been successful in treating many pseudophakic eyes with malignant glaucoma.¹⁴⁶ If laser treatment is unsuccessful, then a pars plana vitrectomy to disrupt the anterior hyaloid face is indicated, with additional reformation of the anterior chamber.

The fellow eye in a patient who has had malignant glaucoma is also at high risk for this condition,^{137,147} particularly in eyes with occludable angles or with partial angle closure. In these cases, some surgeons recommend a peripheral iridotomy prior to any planned surgical procedures, with postoperative atropine and antiglaucoma medications.^{142,143}

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INTRAOCULAR TUMORS AND GLAUCOMA

Christopher D. Pelzek, M.D., and Andrew P. Schachat, M.D.

Correctly diagnosing an intraocular tumor as the cause of glaucoma provides the clinician an opportunity to preserve life, as well as vision. Despite an ever-increasing variety of ancillary tests, a thorough history and ocular examination remain crucial to making the appropriate diagnosis. Approximately 5% of eyes with intraocular tumors develop glaucoma (Table 29-1).¹ The tumors most likely to develop glaucoma include primary tumors of the iris and ciliary body and the choroid and retina, in addition to metastatic tumors and leukemic and lymphoid tumors.

In general, this form of glaucoma is unilateral. Iridociliary tumors are more likely to obstruct aqueous outflow and produce glaucoma than those located more posteriorly. The latter tend to cause glaucoma through anterior segment neovascularization and anterior displacement of the lens-iris diaphragm.

Management is primarily directed toward the malignancy itself. This consists of establishing the underlying diagnosis and includes a search for the primary source in cases of metastatic disease. The complication of glaucoma often indicates advanced disease, and many of these eyes require enucleation. However, many patients respond well to specific radiotherapy or chemotherapy, which can be effective adjuncts to standard medical and surgical glaucoma therapy.

PRIMARY TUMORS OF THE IRIS AND CILIARY BODY (TABLE 29-2)

OCULODERMAL MELANOCYTOSIS (NEVUS OF OTA)

Oculodermal melanocytosis (Chapter 30) is a congenital condition characterized by hyperpigmentation of the episclera, the uveal tract, and the skin in the distribution of the trigeminal nerve, due to increased numbers of

TABLE 29-1 INTRAOCULAR TUMORS AND SECONDARY INTRAOCULAR PRESSURE ELEVATION

Tumor	Total No. Eyes	No. Eyes With IOP Elevation (%)
Uveal melanoma		
Iris melanoma	102	7 (7)
Ciliary body melanoma	96	16 (17)
Choroidal melanoma	1913	32 (2)
Total	2111	55 (3)
Uveal metastasis		
Iris metastases	11	7 (64)
Ciliary body metastases	3	2 (67)
Choroidal metastases	242	3 (1)
Total	256	12 (5)
Retinoblastoma		
Miscellaneous intraocular tumors		
Lymphoma	11	3 (27)
Leukemia	11	1 (9)
Benign reactive lymphoid hyperplasia (choroid)	2	0 (0)
Adenoma, pigment epithelium (iris)	2	1 (50)
Adenoma, pigment epithelium (ciliary body)	1	0 (0)
Adenoma, nonpigment epithelium (iris)	0	0 (0)
Adenoma, nonpigment epithelium (ciliary body)	4	0 (0)
Medulloepithelioma (ciliary body)	2	2 (100)
Melanocytoma (iris)	1	1 (100)
Total	34	8 (24)
Overall Total		
	2704	126 (5)

(From Shields CL, Shields JA, Shields MB, et al. Prevalence and mechanisms of secondary intraocular pressure elevation in eyes with intraocular tumors. *Ophthalmology* 1987;94:839–846.)

TABLE 29-2 MECHANISMS OF GLAUCOMA ASSOCIATED WITH IRIS AND CILIARY BODY TUMORS

Tumor	Mechanism
Oculodermal melanocytosis	Open angle (melanocytic infiltration of TM)
Diffuse iris nevus	Direct extension into TM
Melanocytoma	
Ciliary body	Tumor extension into angle and TM
Iris	Tumor necrosis and pigment dispersion into TM
Iris melanoma	
Circumscribed	Direct extension onto TM Seeding of tumor cells and macrophages into TM
Diffuse	Direct tumor infiltration of the TM
Ciliary body melanoma	Direct infiltration and pigment dispersion into TM
Adenoma/adenocarcinoma	Direct infiltration and pigment dispersion into TM
Medulloepithelioma	Iris neovascularization Tumor infiltration of the TM Peripheral anterior synechiae and angle closure
Juvenile xanthogranuloma	Direct tumor infiltration of the TM Trabecular obstruction by RBCs Anterior displacement of the iris and angle closure
Neurilemoma	Anterior displacement of iris and angle closure

TM, trabecular meshwork; RBCs, red blood cells.

plump, heavily pigmented melanocytes. The condition is predominantly unilateral, with isolated dermal involvement in 35% of cases and only ocular involvement in 6%.²

The diagnosis generally depends on recognizing the macular, blue to black pigmentation of the skin, and the slate gray to brown appearance of the episclera in mottled or confluent patches. Hyperchromic heterochromia is prominent, and diffuse choroidal hyperpigmentation can also occur.

Approximately 10% of individuals can have elevated intraocular pressure (IOP), with glaucomatous damage in nearly 5%.² Although angle-closure and open-angle mechanisms occurred at similar rates in one study, others found open-angle glaucoma in the eye with the more heavily pigmented trabecular meshwork, due to melanocytes within the meshwork itself.^{3,4} Medical management is usually effective, although some cases require laser trabeculoplasty⁵ or, more commonly, filtration surgery.

NEVUS AND MELANOCYTOMA

A nevus is a benign tumor composed of densely packed, slender or plump spindle cells, with varying amounts of melanin pigment that distort the normal tissue architecture. Although their true incidence is unknown, iris nevi occur most often in lightly pigmented irides (Fig. 29-1). In contrast, many ciliary body nevi escape clinical detection and constitute only 6% of posterior nevi.⁶ Although isolated nevi rarely produce secondary glaucoma, diffuse nevi and melanocytomas are exceptions.

Diffuse nevi can occupy either a sector of the iris or the entire iris. In one series, 5 of 7 diffuse iris nevi were associated with glaucoma,⁷ resulting primarily from direct tumor infiltration of the trabecular meshwork.^{7,8} Although

past failures of medical therapy have often resulted in enucleation in such cases, filtration surgery could be considered, given the benign course of most nevi.⁷

The iris nevus syndrome represents a specific form of diffuse iris nevus. This condition arises from proliferation of abnormal corneal endothelium, and 50% of individuals develop glaucoma, usually due to secondary angle closure from contracture of an endothelial membrane. Despite initial medical success, many patients eventually require filtering surgery, which is often successful. Some authorities consider this to be a subset of the iridocorneal endothelial syndrome (Chapter 22).^{9,10}

Melanocytomas, a specific variant of nevi, tend to undergo spontaneous necrosis and fragmentation, which encourages tumor seeding into the angle. In the iris or ciliary body, a melanocytoma usually appears as a darkly

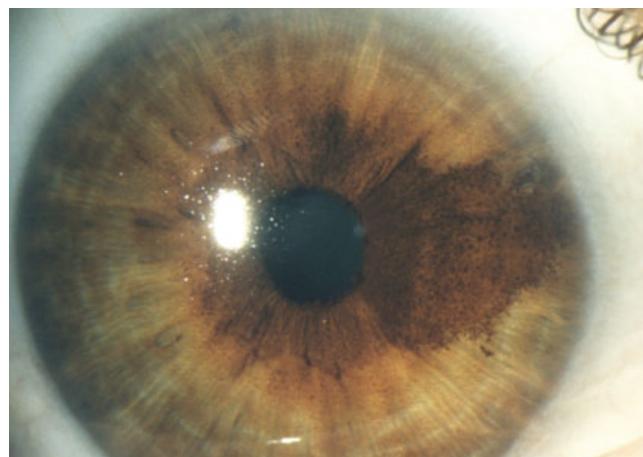


FIGURE 29-1 A stable iris nevus.

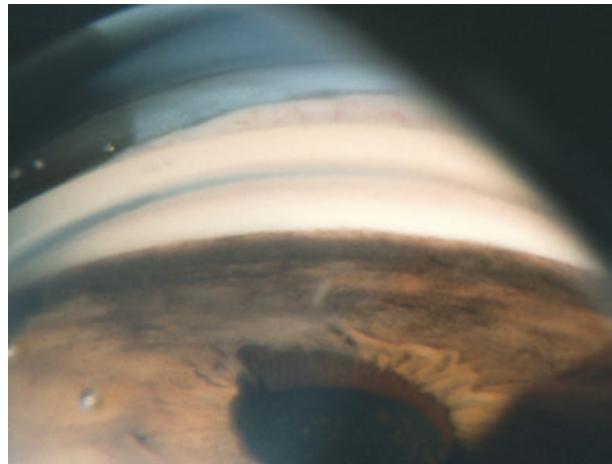
**A****B**

FIGURE 29-2 (A) Iris melanoma with extension into the trabecular meshwork, producing a “ring” melanoma. (B) Evidence of local metastases on the lens capsule and ectropion uvea. The patient later developed a choroidal metastatic lesion with overlying retinal detachment and, ultimately, systemic metastases.

pigmented, circumscribed lesion with dense pigmentation of the trabecular meshwork.^{11–13} Whereas iris melanocytomas most commonly produce open-angle glaucoma by dispersion of pigment and pigment-laden macrophages into the trabecular meshwork,^{11,14} those of the ciliary body usually elevate IOP by direct invasion.^{13,15} Although topical medications generally fail to control IOP, several authors have reported success with sector iridectomy, iridocyclectomy, or partial lamellar sclerouvectomy.^{11,14,15}

MELANOMA

Uveal melanomas are malignant melanocytic tumors, more commonly seen in individuals with light pigmentation and irides.^{16,17} Perhaps because of their anterior location, iris melanomas are diagnosed earlier than ciliary body or choroidal melanomas, generally within the fifth decade of life. Although most iris melanomas consist of the spindle-A or -B cell types, those of the ciliary body can either contain mixed-cell or spindle cell types. The epithelioid type of tumor is much less common in both the iris and the ciliary body.¹⁸

Pathogenesis

Iridociliary melanomas can produce glaucoma by a variety of mechanisms. Glaucoma with circumscribed iris melanoma most commonly results from direct extension of the tumor^{16,19} or by seeding of tumor cells and macrophages into the trabecular meshwork. Although only 7 to 14% of all iris melanomas are associated with secondary glaucoma, glaucoma can occur in over 80% of eyes with diffuse melanoma,^{1,7} primarily from direct tumor infiltration of the meshwork (Fig. 29–2A,B).^{1,19,20} By contrast, the incidence of glaucoma in ciliary body melanoma is 17%,¹ usually due to direct tumor infiltration or pigment dispersion into the trabecular meshwork.^{1,21,22} Any of these tumors can occasionally cause angle-closure glaucoma, either from anterior displacement of the iris or from neovascular glaucoma.^{1,19,21,23}

tion or pigment dispersion into the trabecular meshwork.^{1,21,22} Any of these tumors can occasionally cause angle-closure glaucoma, either from anterior displacement of the iris or from neovascular glaucoma.^{1,19,21,23}

Diagnosis and Differential Diagnosis

Iris and ciliary body melanomas can appear in circumscribed and, less commonly, diffuse forms. In the iris, a circumscribed melanoma usually appears as an elevated, tan to brown mass, occasionally with a fleshy appearance or prominent vascularity (Fig. 29–3).^{17,23} Diffuse melanomas are usually diffusely pigmented, with thickened iris stroma and loss of the iris crypts (Fig. 29–4A,B). Classically, these



FIGURE 29-3 Pigmented iris melanoma with associated, inferotemporal ectropion uvea. Note large episcleral “sentinel” vessel in this region, at the edge of the photograph. A spontaneous hyphema developed in this case, contributing to increased intraocular pressure.

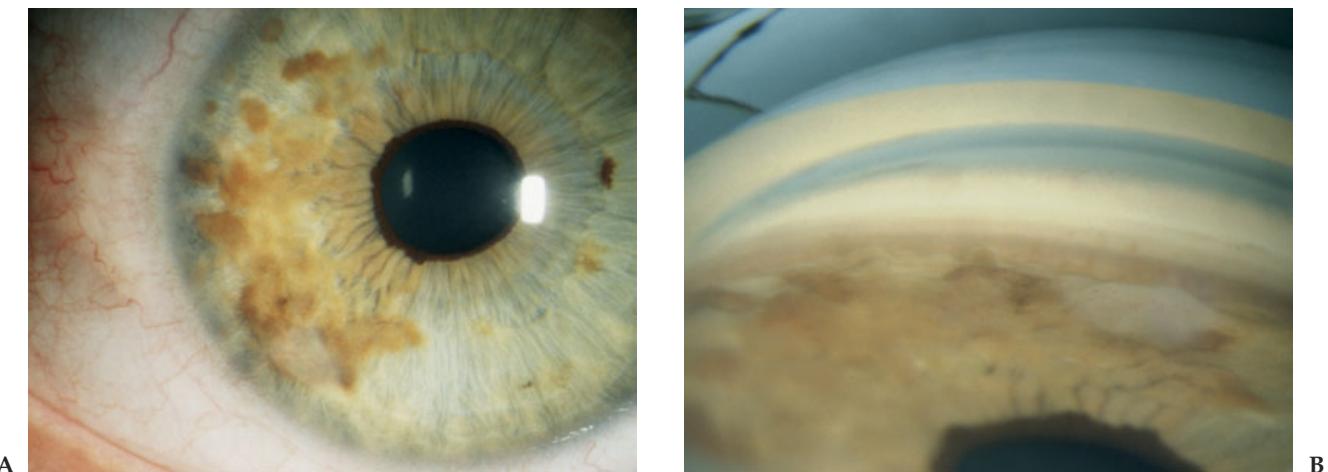


FIGURE 29-4 (A) Diffuse iris melanoma, demonstrating a heterogeneous appearance. (B) Gonioscopic appearance confirms the thickened, irregular nature of this lesion.

patients present with progressive heterochromia and ipsilateral glaucoma.²⁰ Features that distinguish an iris melanoma from a benign nevus include documented growth and distortion of the normal iris architecture, including ectropion uvea. Ciliary body melanomas are generally hidden and may not present until quite large, although they may develop early signs, such as hypotony or dilated episcleral vessels in the involved quadrant (Fig. 29–5).^{18,24}

PEARL... Because of its relatively hidden position, a ciliary body melanoma may not present until it is quite large; however, early signs such as hypotony or dilated episcleral vessels in the involved quadrant may alert the observant clinician.

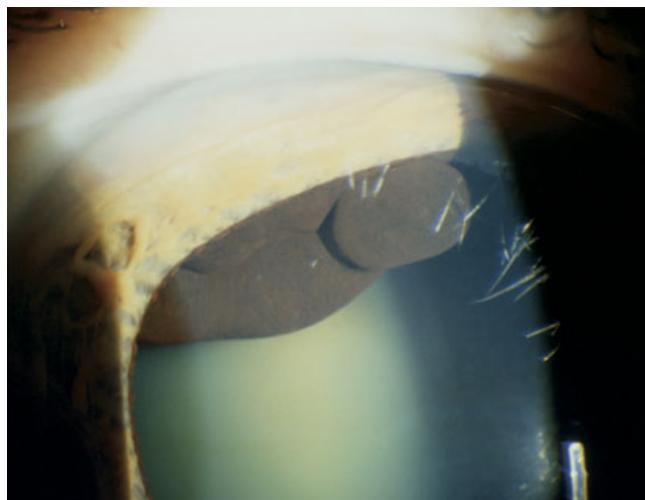


FIGURE 29-5 Ciliary body melanoma. A multinodular ciliary body melanoma is apparent behind the pupil. The lesion was solid echographically.

Several ancillary tests can aid the diagnosis in questionable cases. These include standardized echography for eyes with coexisting posterior lesions, retinal detachments, or vitreous opacity.^{25,26} Although studies disagree on the ability of fluorescein angiography to distinguish iris melanomas from benign lesions,^{24,27} transillumination of the ciliary body can help distinguish melanotic tumors and hemorrhage, which transmit light poorly, from more translucent, nonpigmented tumors.²⁴ When necessary, fine-needle-aspiration biopsy can obtain material for definitive diagnosis.²⁸

Management

Because of their slow growth and benign course, the initial management of most iridociliary melanomas generally consists of periodic observation and slit-lamp photography.^{17,23} Although glaucoma in eyes with a stable, nongrowing iris melanoma can generally be managed medically, eyes with ciliary body melanoma and glaucoma require definitive intervention. In one series, death from metastases occurred in 50% of such individuals within 2 years of diagnosis.²⁴

Eyes with either definite tumor growth or uncontrollable glaucoma generally require surgical intervention. Although a sector iridectomy can eradicate a circumscribed tumor,¹⁷ IOP may remain elevated due to residual neoplastic tissue within the trabecular meshwork. Although diffuse iris melanomas require similar initial management, eyes with evidence of growth or uncontrollable glaucoma generally require enucleation.^{24,29}

For ciliary body melanomas, small or medium tumors may respond to iridocyclectomy,³⁰ partial lamellar sclerouveectomy,³¹ or plaque radiotherapy.³² However, cases with severe glaucoma are better managed by enucleation.³³ Although laser trabeculoplasty and cyclodestructive procedures are alternatives for debilitated patients or those who refuse enucleation, filtering procedures should

be avoided because they can produce local extension and extraocular dissemination of melanoma.³⁴ Rates of metastasis for ciliary body melanoma are higher overall compared with iris melanoma,^{31,35} and increase dramatically when associated with glaucoma.²⁴

PEARL... Eyes with ciliary body melanoma associated with glaucoma require definitive intervention. Up to 50% of these individuals will die from metastatic melanoma arising in the ciliary body within 2 years of diagnosis.

ADENOMA AND ADENOCARCINOMA

These rare tumors can derive from the pigmented epithelium of either the iris or the ciliary body and from the nonpigmented epithelium of the ciliary body. Glaucoma usually results from direct infiltration of the trabecular meshwork by tumor cells^{36–39} and pigment seeding in pigmented lesions.

A tumor of the pigment epithelium usually appears as a dark-gray to black, occasionally multinodular mass, with thickening or anterior displacement of the iris stroma^{36,37,40} and dense pigmentation and tumor infiltration of the trabecular meshwork.^{37,40} Nonpigmented ciliary body epithelial tumors present as gray-white, lobulated masses, associated with thickening or displacement of the iris^{38,41} and lens subluxation, cataract, and uveitis. The differential diagnosis of the pigmented tumors includes melanoma, melanocytoma, and cysts. The presence of uveitis, an irregular contour, and appearance on B-scan ultrasonography⁴¹ may help differentiate nonpigmented ciliary body epithelium tumors from amelanotic melanoma.

The few reported cases associated with glaucoma have been treated by enucleation. However, initial iridectomy, iridocyclectomy, or partial lamellar sclerouvectomy can preserve useful vision in eyes with well-circumscribed tumors and demonstrated growth or uncontrolled glaucoma.^{1,36,40}

MEDULLOEPITHELIOMA

Medulloepithelioma is a congenital tumor arising from the primitive medullary epithelium, with a median age at initial presentation of about 4 years.^{42,43} The nonteratoid variety consists of poorly differentiated neuroepithelial cells, and occasionally Homer-Wright and Flexner-Wintersteiner rosettes. The teratoid variety can include cartilage, rhabdomyoblasts, and neuroglial tissue.^{42,44} Although glaucoma often results from neovascularization of the iris,⁴⁵ other mechanisms include tumor infiltration of the trabecular meshwork⁴² and angle-closure glaucoma with peripheral anterior synechiae secondary to tumor involvement.⁴⁶

The diagnosis of intraocular medulloepithelioma relies primarily on recognizing the clinical constellation of a mass

in the anterior segment, a cataract, and secondary glaucoma (in approximately 30% of cases).⁴² The tumor itself can vary from an isolated white or pink mass to a diffuse membrane overlying the involved structures. Ancillary studies, such as fluorescein angiography and ultrasonography, provide limited benefit in identifying this tumor.⁴⁷

In about two thirds of cases, pain, blindness, or tumor growth prompts primary enucleation.^{42,48} The majority of those treated initially with iridectomy or iridocyclectomy will require eventual enucleation.^{42,45,48} Because of this, and the fact that delayed treatment may allow tumor-related perforation and local extraocular invasion,⁴⁹ only small, well-circumscribed tumors should receive conservative treatment for the tumor and associated glaucoma.

JUVENILE XANTHOGRANULOMA

Juvenile xanthogranuloma is a benign disorder of infants and young children, and, rarely, adults.^{50,51} This condition is characterized by multiple, discrete yellow skin papules, composed of histiocytes, eosinophils, lymphocytes, and multinucleated giant cells^{44,50} that spontaneously regress over time.

The most serious complications of juvenile xanthogranuloma result from involvement of the iris and ciliary body. This may present as a localized iris nodule, or as diffuse iris thickening, producing iris heterochromia. Because these iris lesions are often highly vascularized with thin-walled blood vessels, spontaneous hyphema is common and may often be the presenting sign.^{50,52,53}

Glaucoma is another common presenting sign and may occur in over 80% of cases.⁵² Open-angle glaucoma results from direct tumor infiltration or trabecular obstruction by red blood cells,^{50,52} whereas ciliary body enlargement and anterior displacement of the iris can produce angle-closure glaucoma.⁵⁴

A spontaneous hyphema in a child should always suggest the diagnosis of juvenile xanthogranuloma, particularly when associated with characteristic skin lesions and an iris infiltrate.⁵² Occasionally, difficult cases may benefit from fine-needle-aspiration biopsy and cytological analysis.⁵¹

Treatments for juvenile xanthogranuloma include local excision, oral corticosteroids, and local irradiation.^{51,53–55} Although antiglaucoma medications alone can control IOP in some eyes, many require adjunctive therapy directed at suppressing histiocytic proliferation, such as topical and oral corticosteroids, and even local irradiation. Filtering procedures should be avoided if possible, given the propensity for bleeding in this condition.^{53,55}

NEURILEMOMA

A neurilemoma is a benign, encapsulated tumor arising from the Schwann cells of peripheral nerves. In uveal neurilemomas, the mean age at diagnosis is 38 years, and

only 15% of cases are associated with neurofibromatosis.⁵⁶ Clinically, this tumor, composed of spindle-shaped cells within an abundant collagen matrix,^{44,56} appears as a nonpigmented, smooth ciliary body mass, which may displace the iris anteriorly.^{56–59} With growth, it can further displace the iris-lens diaphragm and produce cataracts and glaucoma.^{58,59}

In the past, the clinical similarity of neurilemoma to amelanotic melanoma has led to enucleation in cases associated with glaucoma. Even now, this distinction remains difficult, in spite of the availability of ultrasonography and fine-needle-aspiration biopsy.⁵⁶ Cases with established, well-circumscribed neurilemomas can be managed with local resection,⁶⁰ and the glaucoma by filtering surgery.⁵⁹

PRIMARY TUMORS OF THE CHOROID (TABLE 29–3)

MELANOMA

Although choroidal melanomas share epidemiological and histologic features with those of the anterior uvea, the median age at diagnosis is about a decade older than that for iris melanoma. Glaucoma, which is more common in larger tumors with associated retinal detachment and inflammation, may result from a variety of mechanisms. The most common of these include neovascular glaucoma (over 50%) and angle-closure glaucoma from anterior displacement of the iris-lens diaphragm (over 30%).¹ Open-angle glaucoma from tumor infiltration or red blood cell seeding of the trabecular meshwork may also occur, along with uveitis.^{1,19}

A choroidal melanoma can appear circumscribed, as an elevated choroidal nodule, or as a diffuse area of thickened choroid. Both varieties can have variable pigmentation.⁶¹ Associated features include ocular inflammation,

TABLE 29–3 MECHANISMS OF GLAUCOMA ASSOCIATED WITH PRIMARY TUMORS OF THE CHOROID

Tumor	Mechanism
Melanoma	Neovascular glaucoma
	Anterior displacement of iris and angle closure
	Direct tumor infiltration and RBC seeding of the TM
	Uveitis
Neurofibroma/ neurilemoma	Anterior displacement of iris and angle closure
	Direct tumor infiltration of the TM
Choroidal hemangioma	Neovascular glaucoma

TM, trabecular meshwork; RBC, red blood cell.

vitreous hemorrhage, choroidal or retinal detachments, and extrascleral extension (see Fig. 29–4A,B).^{62–64}

A fundus contact lens may reveal small serous detachments and pigmentation patterns. Standardized echography constitutes the key ancillary diagnostic test for choroidal melanoma, revealing a characteristic solid, dome-shaped, regularly structured lesion with low/medium internal reflectivity.²⁵ Despite its variability, fluorescein angiography can sometimes help differentiate choroidal melanoma from other lesions, including choroidal metastases and hemangiomas.⁶⁵

Although medical therapy can effectively control non-tumor-related, open-angle glaucoma in patients with small melanomas, the neovascular glaucoma associated with medium or large tumors often necessitates enucleation. Medical and, in particular surgical, glaucoma therapy should be limited to eyes with radiated melanomas, where there is confidence that the tumor is dead.

NEUROFIBROMA AND NEURILEMOMA

A neurofibroma is a benign, nonencapsulated tumor consisting of Schwann cells, fibroblasts, fibrous connective tissue, and, occasionally, axons. These may be isolated or diffuse. Whereas the former appears as a nonpigmented choroidal nodule and resembles a neurilemoma or amelanotic melanoma,^{57,66} the latter presents as multiple, amelanotic, minimally elevated nodules.⁶⁷ A choroidal neurilemoma generally appears as a smooth, minimally pigmented, elevated mass, and may be complicated by cataract or serous retinal detachment.^{57,68,69} Distinguishing either of these entities from an amelanotic melanoma is very difficult, even with fluorescein angiography and ultrasonography.^{24,11,57}

Glaucoma with a choroidal neurofibroma generally results from invasion and obstruction of the trabecular meshwork or anterior iris displacement and angle-closure, usually associated with large tumor size and retinal detachment.^{66,70} A choroidal neurilemoma can produce angle-closure glaucoma through anterior displacement of the iris.^{68,69} Although some well-circumscribed anterior masses can be resected,³¹ neurofibromas and neurilemomas large enough to produce secondary glaucoma generally will require enucleation.

CHOROIDAL HEMANGIOMA

Choroidal hemangiomas may be either circumscribed or diffuse. Whereas the former usually lacks systemic associations, the latter nearly always appears with the cutaneous or central nervous system findings of Sturge-Weber syndrome (Chapters 27 and 30).

A circumscribed choroidal hemangioma is a benign vascular hamartoma. Neovascular glaucoma may complicate as many as 40% of eyes with advanced tumors and retinal detachment.^{71–73} However, secondary glaucoma is

less common in cases with less severe visual disturbances.⁷⁴ Symptoms, when present, appear in the fifth decade. Microscopically classified into capillary, cavernous, or mixed types, depending on the caliber of the predominant blood vessels,^{44,71} the tumor clinically appears as a well-defined, orange-red mass in the macular and peripapillary regions.^{71–73} Black RPE pigment clumps or yellow-gray areas of fibrous proliferation may overlie the mass, along with a serous retinal detachment, which occurs in about 75% of cases. Standardized echography²⁵ and fluorescein angiography⁷² may also aid the diagnosis. Asymptomatic patients require no treatment. Treatment of neovascular glaucoma from choroidal hemangiomas nearly always involves repairing the serous retinal detachment. Although photocoagulation results in subretinal fluid resolution and retinal reattachment in over 90% of cases,^{72,74} some may require cryotherapy or radioactive plaque therapy.

PRIMARY TUMORS OF THE RETINA (TABLE 29–4)

RETINOBLASTOMA

Retinoblastoma is the most common intraocular neoplasm of childhood, with an estimated 200 to 300 new cases reported in the United States each year.⁷⁵ Twenty to 35% of cases are bilateral,^{76,77} in which the average age at diagnosis is 10 to 12 months, as compared with 21 to 25 months for unilateral cases.^{24,76}

Secondary glaucoma is reported to occur in 17 to 23% of retinoblastoma cases.^{1,78} Iris neovascularization occurs in 42 to 72% of these cases, whereas 21 to 26% result from massive serous retinal detachment, anterior displacement of the iris-lens diaphragm, and angle-closure. Tumor seeding with obstruction of the anterior chamber angle is less common.

TABLE 29–4 MECHANISMS OF GLAUCOMA ASSOCIATED WITH PRIMARY TUMORS OF THE RETINA

Tumor	Mechanism
Retinoblastoma	Neovascular glaucoma Anterior displacement of iris and angle closure Tumor seeding of the TM (less common)
Capillary hemangioma	Neovascular glaucoma (total retinal detachment)
Astrocytoma	Anterior displacement of iris and angle closure Neovascular glaucoma (total retinal detachment)

TM, trabecular meshwork.

Clinically, retinoblastomas may exhibit an endophytic, exophytic, or diffuse growth pattern.^{24,77,79} Early lesions appear as white, elevated retinal masses with dilated, tortuous vessels feeding and draining the tumor. In more advanced cases, the friable white tumor may fill much of the posterior chamber and produce leukocoria, along with iris neovascularization and pseudoinflammation, with clusters of tumor cells in the anterior chamber angle (Fig. 29–6A,B).

Useful ancillary diagnostic studies include B-scan ultrasonography⁸⁰ and computed tomography,⁸¹ which help detect tumor calcification and extraocular tumor extension. In addition, magnetic resonance imaging offers excellent contrast resolution for distinguishing retinoblastoma from various simulating lesions.⁸¹

Unilateral cases of retinoblastoma with involvement of nearly the entire retina generally require enucleation.⁸² Other methods, including cryotherapy, photocoagulation, and plaque radiotherapy combined with chemotherapy,⁷⁵ may be indicated in eyes with half of the retina uninvolved, and in the less involved eye of bilateral cases.^{82–84}

In nearly all cases of retinoblastoma associated with secondary glaucoma, the advanced growth of the tumor

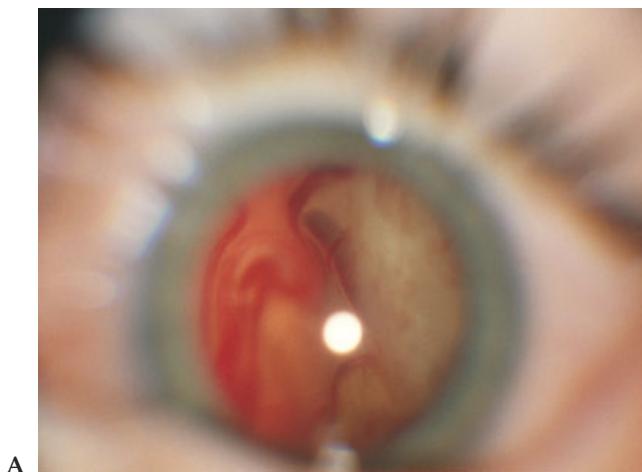
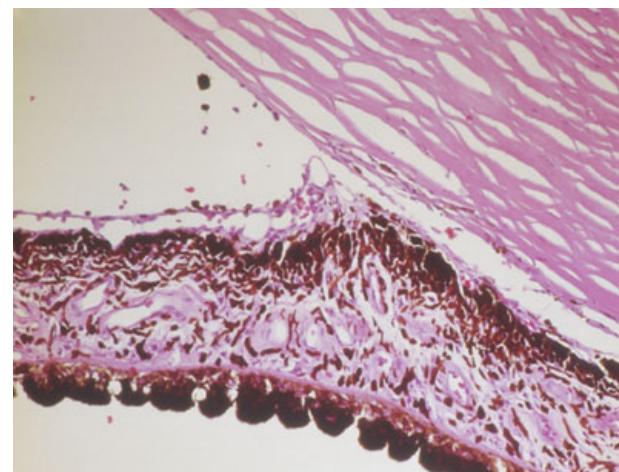


FIGURE 29–6 Retinoblastoma. (A) Leukocoria in an infant with a large retinoblastoma. (B) Enucleated eye from a patient with retinoblastoma and neovascular glaucoma reveals angle closure due to a fibrovascular membrane on the iris surface.



B

results in enucleation of the affected eye. Although continued therapeutic advances have reduced the 5-year mortality rate to 5 to 7%,⁷⁵ the presence of glaucoma implies a reduced life expectancy, given its association with either a large tumor or dissemination,⁸⁵ and the association of iris neovascularization and secondary glaucoma with a higher rate of choroidal and optic nerve invasion.⁸⁶

Uninvolved eyes in patients with unilateral retinoblastoma have an excellent visual prognosis, and effective intervention in bilateral cases provides a reasonable chance for 20/40 or better visual acuity in the better eye.⁸⁴

SPECIAL CONSIDERATION

Iris neovascularization and secondary glaucoma in the presence of retinoblastoma are associated with a higher rate of choroidal and optic nerve invasion.

CAPILLARY HEMANGIOMA

A retinal capillary hemangioma is a benign vascular tumor consisting of capillary-like vessels with endothelial cells and pericytes.^{44,87} Generally diagnosed between the ages of 10 and 30,⁸⁷ this tumor may occur as an isolated lesion or in a multiple or bilateral manner, in which case it is usually associated with von Hippel-Lindau syndrome.

Examination typically reveals a red nodule with dilated, tortuous vessels extending from the mass toward the optic nerve.⁸⁷⁻⁸⁹ Most hemangiomas are surrounded by an area of exudation that enlarges as the tumor grows. Advanced cases may develop a total retinal detachment, providing the setting for the development of neovascular glaucoma.^{88,89}

Cryotherapy and photocoagulation in tumors less than 2.5 disc diameters can improve vision by promoting absorption of subretinal fluid in the macular region,^{87,90} and avert the risk for late-onset glaucoma by preventing retinal detachment. Unfortunately, cases with neovascular glaucoma often have extensive retinal damage and ultimately poor vision.

ACQUIRED ASTROCYTOMA

Unlike astrocytic hamartomas associated with tuberous sclerosis, an acquired retinal astrocytoma has no cutaneous or central nervous system manifestations. This tumor is composed of whorls of fusiform or polygonal astrocytes with an eosinophilic, fibrillar cytoplasm.⁹¹ Clinically, a white-pink retinal mass with superficial blood vessels extends into the vitreous, most often near the optic nerve head.^{91,92}

Progressive enlargement of the tumor can produce anterior iris displacement and acute angle-closure glaucoma.⁹¹ Continued growth of the tumor and increasing

exudative material can also contribute to extensive serous retinal detachment, setting the stage for neovascular glaucoma.^{92,93}

In spite of fluorescein angiography and ultrasonography, establishing a clinical diagnosis without associated systemic disease remains difficult, and suspicion of retinoblastoma or choroidal melanoma often leads to enucleation. All reported cases associated with secondary glaucoma have required enucleation, usually due to severe retinal damage and visual loss.⁹¹⁻⁹³

METASTATIC TUMORS

Once considered rare, metastatic tumors to the eye are the most common form of intraocular malignancy.⁹⁴ Arising most commonly from the breast, lung, skin, and gastrointestinal tract,^{95,96} ocular metastases frequently target the choroid. However, metastases to the anterior uvea are more likely to produce secondary glaucoma. Although large studies have found a 5 to 7.5% incidence of glaucoma in cases involving metastatic carcinoma to the eye, the incidence of glaucoma can be as high as 65% in cases involving the iris and ciliary body and only 1% for metastases to the choroid.^{1,94,97} Isolated retinal and optic nerve metastases are much less common, with only a few reported cases of secondary glaucoma.⁹⁸⁻¹⁰⁰ The histologic appearance of ocular metastases varies with the site of the primary tumor.

SPECIAL CONSIDERATION

Fifty-six to 65% of eyes with metastatic carcinoma to the iris and ciliary body can develop secondary glaucoma as opposed to only 1% of eyes with choroidal metastases.

PATHOGENESIS

Ocular metastases can produce glaucoma through several mechanisms. Iridociliary metastases can cause open-angle glaucoma through mechanical obstruction of the angle, direct tumor infiltration of the trabecular meshwork, or obstruction of the trabecular meshwork by tumor cells, inflammatory cells, and erythrocytes.^{1,97,101-103} Angle-closure glaucoma arises from anterior displacement or thickening of the iris as well as the development of peripheral anterior synechiae.^{1,97,104}

Whereas iridociliary metastases directly involve the anterior chamber angle and are more likely to produce glaucoma at an earlier stage, secondary glaucoma associated with choroidal and retinal tumors usually appears only after diffuse chorioretinal infiltration or extensive retinal or choroidal detachment.^{1,98-100,105} Such cases usually result from neovascularization or angle-closure due to anterior displacement of the lens-iris diaphragm.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Metastatic carcinomas to the anterior segment often appear as a white-yellow, gelatinous isolated nodule, or a diffuse lesion (Fig. 29-7).^{96,97,101} Inflammatory cells, red blood cells, and tumor cells may seed the anterior chamber and produce a pseudohypopyon or lodge in the trabecular meshwork. In contrast, anterior uveal melanomas produce a dark-colored hypopyon, composed of necrotic tumor cells and pigment-laden macrophages.¹⁰² Ciliary body metastases frequently escape early detection, often remaining undiscovered behind the iris until severe visual loss or glaucoma develops.^{106,107}

In the choroid, metastatic carcinomas usually have a creamy yellow appearance,^{96,108} whereas metastatic melanomas are more gray to brown.^{96,103} Both may appear as single lesions or multifocal plaques in the posterior segment. In the retina, metastatic carcinomas and melanomas both present as tissue plaques with intraretinal exudates or hemorrhages, although the former appear yellow-white and the latter gray-brown.^{98,100,109} Retinal metastases commonly involve the vitreous, varying from white tumor cells in carcinomas to yellow-brown tumor globules in melanomas.

Detecting the primary tumor requires a comprehensive history and ocular examination, and a thorough systemic evaluation that includes appropriate imaging and laboratory tests. Ancillary diagnostic tests of the intraocular tumor itself include ultrasonography and fluorescein angiography, which may help distinguish a metastatic lesion from melanoma.^{25,110} Computed tomography and magnetic resonance imaging can help define the extent of tumor. If the diagnosis remains uncertain, fine-needle-aspiration biopsy of aqueous humor, vitreous, and occasionally the tumor itself can provide important material for cytopathologic examination.¹⁰²

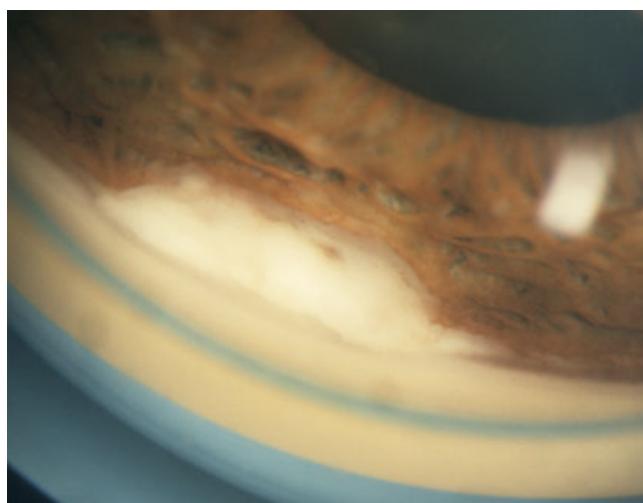


FIGURE 29-7 Metastatic lesion of the superior angle in a patient with known lung carcinoma.

MANAGEMENT

The initial treatment of ocular metastases and glaucoma generally involves chemotherapy or other systemic therapy recommended for the primary tumor.^{96,111} External beam or, less frequently, plaque radiotherapy may be used if the tumor continues to grow or if it threatens visual function, such as with foveal involvement.^{112–114} Cases of glaucoma that do not respond to these treatments should receive maximal medical therapy and, occasionally, filtering surgery to control the IOP. Rarely, intractable pain necessitates palliative enucleation.¹⁰⁵

LEUKEMIA AND LYMPHOID TUMORS

Leukemia and lymphoid tumors can involve all intraocular structures, especially the uveal tract. Clinical studies have revealed intraocular leukemic infiltrates in approximately 3% of leukemic patients, whereas 39 to 50% develop secondary changes from hematologic abnormalities.¹¹⁵ Lymphoid tumors, such as benign reactive lymphoid hyperplasia and primary intraocular lymphoma (reticulum cell sarcoma), may also locally or diffusely involve any intraocular structure.^{116,117} Intraocular lymphoma, which occurs primarily in older adults, is often associated with systemic lymphoma, and over 50% of cases eventually develop central nervous system involvement.^{117,118}

PATHOGENESIS

Histologically, leukemia and intraocular lymphoma present a diffuse infiltration of the uvea or retina by the characteristic neoplastic lymphocytes.^{44,119} In lymphoid hyperplasia, the uvea is diffusely thickened by an infiltrate of mature lymphocytes and plasma cells with areas of interstitial eosinophilic material.¹¹⁶

Secondary glaucoma associated with leukemia and lymphoid tumors reflects the diffuse tissue involvement and tumor seeding characteristic of these malignancies. Although infiltration of the trabecular meshwork by tumor cells can cause open-angle glaucoma,^{116,120,121} angle closure generally results from chronic iridocyclitis and peripheral anterior synechiae.^{116,120,122} Other causes of angle-closure glaucoma include diffuse ciliary body involvement, resembling a ring melanoma,¹¹⁶ and, less commonly, neovascular glaucoma that is usually accompanied by extensive chorioretinal infiltration or retinal necrosis.¹²⁰

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The clinical ocular features of these tumors depend on their site of involvement. In the anterior segment, the iris stroma may be diffusely thickened or contain localized tumor nodules.^{116,120} Aqueous cells and keratic precipitates

are common, and pseudohypopyon can develop in severe cases, contributing to elevated IOP.^{121,123} In the posterior segment, leukemia produces white-yellow leukemic cell infiltrates in the retina and choroid, along with intraretinal hemorrhages, cotton-wool spots, and white-centered hemorrhages.^{115,119} Lymphoid hyperplasia of the posterior segment generally appears as nodular or diffuse choroidal thickening, often with a serous retinal detachment.^{116,122,124} In contrast, intraocular lymphoma can cause perivascular retinal infiltrates with a marked vitritis,^{117,125} or white-yellow choroidal plaques with minimal vitreous inflammation.¹²⁵

Because ancillary ophthalmic studies such as fluorescein angiography and ultrasonography provide little specific information,^{24,126} the medical history and systemic evaluation are vital to confirming the diagnosis of leukemia or lymphoma. Although fine-needle-aspiration biopsy for cytopathological analysis of aqueous or vitreous cells can confirm the diagnosis in uncertain cases,^{121,127} repeat biopsies may be necessary.¹¹⁸

MANAGEMENT

Initial therapy for suspected benign reactive lymphoid hyperplasia consists of local or systemic corticosteroids,^{122,128,129} followed, if necessary, by low-dose ocular irradiation.^{124,130} With intraocular lymphoma and leukemia, ocular radiotherapy can be added to the appropriate chemotherapy for the underlying systemic disease.^{118,119,121} In patients with glaucoma, radiotherapy can also effectively normalize the IOP,^{121,131} which is frequently unresponsive to antiglaucoma medical therapy alone.^{124,131} Occasionally, the IOP remains elevated immediately after irradiation due to obstructed aqueous outflow by necrotic debris. These cases require an anterior chamber washout.¹²³ Some refractory eyes become blind and painful despite all of these interventions, and are eventually enucleated.

PEARL... Although initial medical management often fails to control glaucoma associated with leukemia or lymphoid tumors, radiotherapy can lower IOP to normal levels within days.

In leukemia and benign reactive lymphoid hyperplasia, the prognosis for vision varies with the extent and duration of the disease, and early treatment generally produces a favorable outcome.^{128,129} With primary intraocular lymphoma, prompt treatment can also result in improved visual acuity.^{117,118} However, the diagnosis in this condition is often delayed and extensive chorioretinal involvement and persistent uveitis usually limit final vision, despite effective treatment of the tumor itself.^{24,117,130}

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SYSTEMIC DISEASES AND GLAUCOMA

Andreas Katsuya Lauer, M.D., and John C. Morrison, M.D.

Correlations between systemic diseases and glaucoma date back to 1792, when Georg Josef Beer of Vienna first ascribed the symptoms and findings of acute glaucoma to an arthritic eye inflammation of gouty origin.¹ He contended that patients with true gout could develop glaucoma even without inflammation.^{2,3} Although this association was soon abandoned, investigators continue to link glaucoma to a growing list of systemic diseases.

Some systemic diseases have well-established relations with glaucoma, whereas in many others, the connection to glaucoma is less certain. This chapter collates the systemic conditions in which glaucoma has been reported (Table 30-1), along with possible mechanisms, which are detailed in Tables 30-2 through 30-9. Other chapters contain a more thorough discussion of some entities. Discussions of management, which usually depends on the underlying mechanism, are generally referred to other chapters devoted to these mechanisms.

VASCULAR DISEASE

Carotid artery insufficiency, ophthalmic artery insufficiency, and retinal vascular occlusive disorders can all cause neovascular glaucoma. In addition, orbital or cavernous sinus arteriovenous (AV) malformations or thromboses can affect intraocular pressure (IOP) by elevating episcleral venous pressure. Because Chapters 21, 23, and 27 address these entities in detail, the following discussion will concentrate on the relationship between glaucoma and blood pressure.

BLOOD PRESSURE

Many investigations have implicated blood pressure as an important risk factor for glaucoma.⁴⁻⁶ Recent epidemi-

ological and ambulatory blood pressure monitoring studies (Chapter 1) have correlated systemic blood pressure with elevated IOP and glaucoma.⁷⁻¹⁰ However, the exact relationship between these conditions remains unclear because both high and low blood pressure can coexist with elevated IOP and glaucoma.⁸ This paradox suggests that vascular considerations may relate to glaucoma through the interactions of systemic arterial pressure, IOP, and autoregulation of the optic nerve head, as opposed to IOP alone.⁸⁻¹¹

The microvasculature sustains the metabolic requirements of the optic nerve head by autoregulating blood flow resistance and velocity across a wide range of IOPs and systemic arterial pressures (Chapter 8). Chronic hypertension, where microangiopathic changes increase resistance to perfusion, could alter these compensatory mechanisms, lower the injury threshold, and increase the susceptibility of the optic nerve head to both IOP and hemodynamic changes.

However, periodic hypotension, which decreases perfusion, may also lead to progressive glaucomatous nerve damage.^{8,10} Monitoring studies have demonstrated that normal subjects experience a nocturnal decrease in blood pressure between 2 and 4 AM. These nocturnal blood pressure "dips" are greater in patients with normal tension glaucoma (NTG) and in patients taking antihypertensive medication. These patients tend to suffer progressive visual field deficits, and multiple episodes of low systemic blood pressure may produce glaucomatous optic neuropathy despite adequate IOP control.¹⁰⁻¹²

CEREBROVASCULAR DISEASE

Although glaucoma is infrequently associated with neurological disease,¹³ some cases of NTG may result from vasospasm, particularly in patients with migraine.¹⁴ (Chapters 1 and 15).

TABLE 30-1 SYSTEMIC DISEASES AND GLAUCOMA

Vascular diseases	Toxoplasmosis
Carotid artery insufficiency	Onchocerciasis
Retinal vascular occlusive disorders	Toxocariasis
Arteriovenous malformations	Coccidioidomycosis
Blood pressure	Phakomatoses (Table 30-5)
Cerebrovascular disease	Sturge-Weber (encephalotrigeminal angiomas)
Endocrine diseases (Table 30-2)	Klippel-Trenaunay-Weber
Diabetes mellitus	Neurofibromatosis Type 1 (von Recklinghausen disease)
Thyroid diseases	Von-Hippel-Lindau
Cushing's syndrome	Nevus of Ota (oculodermal melanocytosis)
Pituitary disease	Pigmentovascularis
Autoimmune diseases	Diffuse congenital hemangiomatosis
Dermatologic and connective tissue diseases	Wyburn-Mason syndrome
Cicatricial pemphigoid	Tuberous sclerosis
Scleroderma	Metabolic diseases (Table 30-6)
Poikilodermatomyositis ⁵⁰	Systemic congenital anomalies (Table 30-7)
Ehlers-Danlos	Chromosomal anomalies
Osteogenesis imperfecta	Congenital syndromes with goniodysgenesis
Renal diseases	Stickler's syndrome
Cystinosis	Marfan's syndrome
Familial nephropathy, retinitis pigmentosa, closed-angle glaucoma	Weill-Marchesani
Renal transplant recipients	Prader-Willi
Hematologic diseases	Hallerman-Streiff
Sickle cell hemoglobinopathy (Table 30-3)	Retinopathy of prematurity
Essential thrombocythemia	Primary familial amyloidosis
Hematologic malignancies	Radiotherapy
Infectious diseases (Table 30-4)	Charged-particle external beam
Herpes simplex	Episcleral plaque brachytherapy
Varicella zoster virus	Thermotherapy
Mumps	Drugs
Adenovirus serotype 10 keratoconjunctivitis	Corticosteroids
Rubella	Nonsteroidal drugs (Tables 30-8, 30-9)
Cytomegalovirus	Intracarotid chemotherapy
Hansen's disease	Teratogens (alcohol, thalidomide)
Syphilis	

TABLE 30-2 ENDOCRINE DISEASES AND GLAUCOMA

Disease	Mechanism
Diabetes mellitus	Neovascular glaucoma Open angle Angle closure
Thyroid-associated orbitopathy	Orbital congestion Elevated episcleral venous pressure
Hypothyroidism	Decreased trabecular outflow Normal-tension glaucoma
Cushing's syndrome	Steroid-induced glaucoma
Pituitary disease	Steroid-induced glaucoma (Disc cupping due to optic nerve compression)

ENDOCRINE DISEASES

Glaucoma can accompany several endocrine disorders (Table 30-2). Although causality is often uncertain, these associations have prompted many studies into how

endocrine mechanisms can regulate aqueous humor dynamics.¹⁵

DIABETES MELLITUS

Diabetes mellitus (DM) can occur with primary open-angle glaucoma (POAG), angle-closure glaucoma, or it can cause neovascular glaucoma.

Neovascular Glaucoma

One third of patients with neovascular glaucoma (NVG) have proliferative diabetic retinopathy, and the connection between these two entities is well established (Chapter 21). Although reducing the vasoproliferative stimulus by ablating the retina with photocoagulation or cryotherapy is the cornerstone in preventing NVG, many patients still require trabeculectomy with antimetabolites, drainage tube implantation, or cycloablation to control IOP. Additional complicating factors include cataract extraction or posterior capsulotomy, and traction retinal detachment.¹⁶

Open-Angle Glaucoma

The association between POAG and diabetes remains controversial (Chapters 1 and 15).¹⁶ Recent population-based studies disagree on whether there is a correlation between correlate diabetes and POAG.^{18–20,21–23} Diabetics have a higher prevalence of POAG, ocular hypertension, steroid-induced glaucoma, and enlarged cup-to-disc ratios. However, comparisons of optic disc morphology do not consistently show a difference between diabetics and nondiabetics, except that the former have decreased visible nerve fiber layer and increased optic disc pallor.¹⁶ This could simply result from diabetic microangiopathy.

CONTROVERSY

Although DM may predispose to POAG through several theoretical mechanisms, epidemiological studies do not agree on a definite relationship.

Autonomic dysfunction and osmotic attraction of fluid into the intraocular space induced by hyperglycemia could explain an association between diabetes and glaucoma.^{18,16} These include diabetic microangiopathy in the optic nerve head that may also lead to ischemic injury or endoneurial dysfunction and influence visual field loss.²⁴ In general, the treatment for POAG in diabetics follows the guidelines presented in Chapter 15. However, the practitioner must remember that beta-blocking agents can block the patient's response to hypoglycemia. In addition, trabeculectomy and diabetics can be accompanied by greater post-operative inflammation and a higher rate of filter failure.¹⁰

Angle-Closure Glaucoma

Angle-closure glaucoma (see also Chapter 16) in diabetics generally results from pupillary block. This may be phacomorphic, due to increased lens thickness and sorbitol-induced osmotic lens swelling. Treatment includes laser iridotomy, reducing ocular inflammation, and controlling hyperglycemia.¹⁶ Occasionally, removal of a markedly intumescent lens is necessary.

Following cataract surgery, diabetics can still develop pupillary block, even with posterior chamber intraocular lenses. This probably results from posterior synechiae due to increased inflammation and a relatively nonpliable iris. Diabetics with pseudophakia warrant continued observation, and prompt laser iridotomy, should pupillary block develop.

Angle closure without pupillary block may occur following treatment of diabetic retinopathy by pan retinal photocoagulation (Chapter 16).

THYROID DISEASE

An increased prevalence of ocular hypertension and glaucoma can occur in both hyper- and hypothyroidism.¹⁵

Thyroid-associated orbitopathy, which can be independent of the patient's thyroid status, and hypothyroidism both appear related to glaucoma.

Thyroid-Associated Orbitopathy

Thyroid-associated orbitopathy (TAO) (Chapter 23) or Graves' ophthalmopathy, is an autoimmune, organ-specific disease characterized by inflammation, edema, and secondary fibrosis of the orbital tissues. Stimulated orbital fibroblasts produce glycosaminoglycans and collagen in the orbit^{25,26} leading to variable amounts of proptosis, eyelid edema and retraction, conjunctival injection, chemosis, exposure keratopathy, corneal ulceration, extraocular dysmotility, and optic neuropathy (Fig. 30-1). Although most frequent in hyperthyroid patients, Graves' ophthalmopathy also occurs in euthyroid and hypothyroid patients. The systemic and ophthalmic manifestations generally run independent courses.^{27,28}

The infiltrative orbital process and enlarged extraocular muscles can produce elevated IOP directly through pressure on the globe, and indirectly through compression of the ophthalmic veins and elevated episcleral venous pressure.³⁰ Because the inferior rectus is most commonly involved, restricted movement of this muscle frequently elevates IOP in upgaze.^{31,32} Prolonged, active, thyroid-associated orbitopathy with ocular hypertension can progress to glaucomatous damage.²⁹ Treatment usually begins with medical management. It may also include direct treatment of the orbitopathy and even filtration surgery, which carries an increased risk of postoperative complications.

Hypothyroidism

Ophthalmic features of hypothyroidism include chemosis, periorbital edema, blepharoptosis, and loss of the outer third of the eyebrows.²⁷ Some patients develop myxedema, an extracellular accumulation of hydrophilic glycosamino-

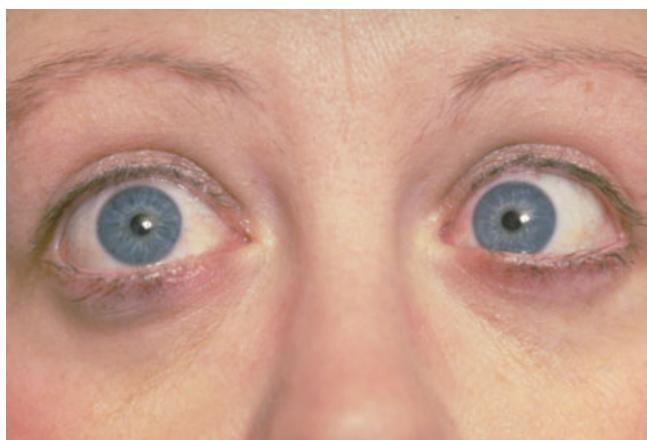


FIGURE 30-1 A patient with eyelid retraction and restrictive strabismus due to thyroid-associated orbitopathy. The right optic nerve head demonstrated glaucomatous cupping.

glycans in the dermis. Subclinical cases require laboratory testing to establish the diagnosis.²⁸

Some hypothyroid patients may develop glaucoma secondary to thyroid-associated orbitopathy. Others lack orbital congestion and present a clinical picture similar to POAG.^{33,34} Studies of patients with newly diagnosed hypothyroidism have shown that 23% had POAG or ocular hypertension. Among patients with POAG, 23% had hypothyroidism, 11% of whom were undiagnosed.^{34–36}

PEARL... Hypothyroidism should be considered in patients with newly diagnosed primary open-angle glaucoma or uncontrolled open-angle glaucoma.

Although precise mechanisms are unclear, dysregulation of the extracellular matrix in the hypothyroid state may result in accumulation of glycosaminoglycans in the trabecular meshwork.³⁷ Treatment of the hypothyroid state with thyroxine may restore extracellular matrix metabolism in some patients, increase aqueous outflow, and reduce IOP.^{33,34} An autoimmune mechanism has also been proposed for certain patients with NTG. In one study, over 10% of NTG patients had hypothyroidism.³⁸

CUSHING'S SYNDROME

Elevated plasma cortisol or noncortisol glucocorticoids in patients with glaucoma and ocular hypertension has led some investigators to associate glaucoma with dysfunction of the hypothalamic-pituitary-adrenal axis.^{15,39} Patients with Cushing's syndrome (see also Chapter 18) may secrete excess cortisol through primary hyperadrenalinism (adrenal tumors or adrenal hyperplasia), secondary hyperadrenalinism [excess adrenocorticotrophic hormone (ACTH) from pituitary tumors or hypothalamic dysfunction], or from circulating ACTH-like substances involved in the paraneoplastic effects of bronchogenic, thymus, and pancreatic tumors. Elevated IOP or increased diurnal variation in IOP can occur with excess ACTH^{39–40} or adrenal adenoma,⁴¹ and may normalize following adrenalectomy (Chapter 18).⁴¹

PITUITARY DISEASE

POAG and elevated IOP have also been reported in patients with pituitary tumors.^{42,43} Steroid-induced glaucoma from excess ACTH has already been discussed. In patients with acromegaly, connective tissue deposition from excess growth hormone may reduce aqueous outflow.⁴² However, increased corneal thickness in these patients may increase corneal rigidity and artificially elevate applanation measurements.^{44,45}

Compression of the visual tract by a pituitary adenoma may also cause optic disc cupping, which typically

appears asymmetric.⁴⁶ These patients require screening examinations to rule out glaucoma as a cause of optic nerve damage.

AUTOIMMUNE DISEASES

Patients with uveitis from autoimmune or collagen vascular disorders can develop open-angle and angle-closure glaucoma. Treatment of uveitic glaucoma frequently requires topical, regional, or systemic corticosteroids that may also cause glaucoma in susceptible individuals (Chapter 26).

DERMATOLOGIC AND CONNECTIVE TISSUE DISEASES

Glaucoma infrequently occurs in association with dermatologic disorders. Glaucoma in neurofibromatosis and Sturge-Weber syndrome is discussed in the following text and in Chapter 23. Chapter 26 reviews glaucoma associated with Hansen's disease and Vogt-Koyanagi-Harada syndrome, whose primary mechanism of glaucoma is uveitis. Other dermatologic conditions associated with glaucoma include cicatricial pemphigoid, scleroderma, poikilodermatomyositis,⁵⁰ osteogenesis imperfecta, and Ehlers-Danlos syndrome.

CICATRICIAL PEMPHIGOID

Glaucoma can occur in 26% of patients with cicatricial pemphigoid.⁴⁷ This is a systemic disease of progressive scarring due to autoantibodies directed at the basement membrane of the mucosal epithelium, and, less often, the skin. Ophthalmic findings include chronic conjunctivitis and fibrosis, fornix foreshortening, symblepharon, keratitis sicca, corneal vascularization, and corneal keratinization (Fig. 30-2). Potential mechanisms of elevated IOP include reduced outflow from chronic inflammation and scarring of the episclera.



FIGURE 30-2 Cicatricial pemphigoid, demonstrating conjunctival scarring and foreshortening of the inferior fornix.

Evaluation and management of glaucoma in this condition is difficult. Corneal scarring limits the accuracy of tonometry, visual field assessment, and examination of the optic nerve head. In addition, topical glaucoma drops may aggravate the inflammatory process. Because conjunctival inflammation and scarring can diminish the success of filtration surgery,⁴⁷ adjunctive oral immunosuppressants, usually prescribed by an internist or dermatologist familiar with their use, should precede any surgical procedure on these patients.

Many patients receive chronic topical glaucoma agents long before the diagnosis of cicatricial pemphigoid. Echothiophate iodide, pilocarpine, idoxuridine, epinephrine, timolol maleate, dipivefrin hydrochloride, and practolol can all induce a pemphigoid-like conjunctival reaction, or "pseudopemphigoid." These patients lack the extraocular features of pemphigoid, and stopping the glaucoma agents generally arrests the cicatrizing process. Studying a conjunctival biopsy by immunofluorescence to detect autoantibodies will usually confirm the diagnosis of true pemphigoid.

PITFALL... Glaucoma may occur in 26% of patients with cicatricial pemphigoid. However, this diagnosis must be distinguished from pseudopemphigoid, which may result from chronic therapy with many ocular hypotensive drops.

SCLERODERMA

Scleroderma is a connective tissue disorder of unclear etiology characterized by fibrous degenerative changes of the skin in patients between 30 and 50 years of age. Glaucoma has been associated with the localized linear form of scleroderma, and patients with a *coup de sabre* lesion of bandlike linear atrophy of the forehead and periorbital skin may exhibit heterochromia iridis or defects in iris transillumination. A few patients are reported to have pigmentary glaucoma.^{48–49}

EHLERS-DANLOS SYNDROME AND OSTEogenesis IMPERFECTA

Ehlers-Danlos syndrome and osteogenesis imperfecta are inherited conditions of abnormal collagen formation with the main ocular features of corneal thinning and blue sclerae. Whereas open-angle glaucoma and glaucoma following trauma may occur in Ehlers-Danlos syndrome,^{51,52} mechanisms of glaucoma in the latter remain unclear.⁵³

RENAL DISEASES

Elevated IOP has been reported in 5 to 47% of renal transplant recipients, 2 to 25% of whom develop glaucomatous visual field deficits or cupping. Many of these cases may represent steroid induced glaucoma because these patients invariably receive systemic corticosteroids.^{54–57} This underscores the need for periodic ophthalmic exam-

inations in these patients, and in all patients receiving chronic corticosteroid therapy.

HEMATOLOGIC DISEASES

Sickle cell hemoglobinopathy, hypercoagulable states, and hematologic malignancies are the most likely disorders in this category to produce glaucoma.

SICKLE CELL HEMOGLOBINOPATHY

Sickle cell hemoglobinopathy is a genetic error in the synthesis of the beta-globin chain of hemoglobin. Under conditions of hypoxia or acidosis, this abnormal hemoglobin transforms red blood cells into rigid, elongated crescents that have difficulty passing through the microvasculature and the trabecular meshwork.

These alterations can produce glaucoma by several mechanisms (Table 30–3), including neovascular glaucoma from retinal ischemia and proliferative sickle cell retinopathy (Fig. 30–3A), and hemolytic and ghost cell glaucoma following trauma and spontaneous vitreous hemorrhage. Traumatic or surgically induced hyphema may also lead to a devastating secondary glaucoma because the sickled erythrocytes are incapable of passing through the trabecular meshwork. Small amounts of hemorrhage or a small percentage of sickled erythrocytes can produce marked IOP elevation.⁵⁸ The hyphema exacerbates the already low pO₂, low pH, high pCO₂, and high ascorbate of the aqueous, and helps maintain the sickled configuration.⁵⁹

In addition to IOP elevation, the rigid red blood cells, sluggish flow, and increased blood viscosity can further compromise oxygen delivery to the optic nerve head. This can produce rapid, irreversible deterioration of visual function in these patients.^{60,61}

PEARL... Hyphema patients with a positive sickle cell prep require vigilant and aggressive management should glaucoma develop.

Patients of African American, Hispanic, or Mediterranean extraction with hyphemas require vigilance and aggressive management. This includes performing a rapid sickle cell preparation (solubility screening test) immediately, followed by the more time-consuming hemoglobin

TABLE 30–3 TYPES OF GLAUCOMA IN SICKLE CELL DISEASE

Type	Mechanism
Traumatic	Hyphema, angle recession, trabecular injury
Neovascular	Proliferative sickle cell retinopathy, neovascular glaucoma
Hemolytic	Vitreous hemorrhage
Ghost Cell	Vitreous hemorrhage
Optic nerve head hypoperfusion	Anemia, poor red blood cell passage, elevated intraocular pressure

electrophoresis. If the sickle cell prep is positive, IOP measurements every 6 hours around the clock have been recommended, along with concurrent cycloplegics, aqueous suppressants, and corticosteroids.⁵⁹ Although a single administration of carbonic anhydrase inhibitors or mannitol may help lower pressure, repeated dosage can cause metabolic acidosis and exacerbate erythrocyte sickling.⁶¹ Some authors recommend anterior chamber paracentesis in patients with IOPs exceeding 24 mm Hg for 24 hours, or pressures greater than 30 mm Hg, reserving anterior chamber wash-out for larger hyphemas.⁵⁹ Chapter 27 also discusses the management of this condition.

HYPERCOAGULABILITY

Some studies suggest that abnormal composition, viscosity, or coagulation of the blood can contribute to glaucomatous optic neuropathy by altering the perfusion of the optic nerve head (Fig. 30–3B).^{62–64} Essential thrombocythemia has been associated with central vein occlusion and neovascular glaucoma.⁶⁵ Another group has observed activation of the coagulation cascade and fibrinolysis pathway, with elevated levels of prothrombin fragments and D-dimer in patients with untreated POAG. These alterations may contribute to the increased prevalence of retinal vein occlusion in glaucoma patients.⁶⁶ The clinical appearance of these conditions dif-

fers significantly from that of poor retinal perfusion secondary to carotid insufficiency (Fig. 30–3C).

HEMATOLOGIC MALIGNANCIES

Hematologic malignancies (see also Chapter 29), such as lymphoma and leukemia, may produce glaucoma through outflow obstruction by intraocular infiltration, and may cause secondary glaucoma if orbital involvement elevates episcleral venous pressure.

INFECTIOUS DISEASES

Glaucoma may accompany several infectious diseases, usually due to uveitis (Table 30–4). Most of these conditions are discussed in Chapter 26.

PHAKOMATOSES

The phakomatoses are a diverse group of disorders in which disseminated hamartomas affect the eye, central nervous system, skin, and internal organs.⁶⁷ Glaucoma is a common feature of encephalotrigeminal angiomyomatosis (Sturge-Weber syndrome) and occasionally accompanies neurofibromatosis Type I (von Recklinghausen syndrome) (Table 30–5).



FIGURE 30-3 Systemic conditions that can cause neovascular glaucoma by decreasing retinal perfusion. (A) The peripheral retina of a patient with sickle cell disease demonstrates retinal neovascularization and arteriovenous communication between perfused and nonperfused retina. (B) Widespread, scattered intraretinal hemorrhages and dilated, tortuous retinal veins in a patient with Waldenstrom's macroglobulinemia and hyperviscosity that eventually led to a central retinal vein occlusion. (C) Ocular ischemia from carotid artery disease in an eye with narrowed, easily collapsed retinal arteries and mild intraocular inflammation, progressive cataract, and rubeosis.

TABLE 30-4 INFECTIOUS DISEASES ASSOCIATED WITH GLAUCOMA

<i>Class Condition (Organism)</i>	<i>Mechanism of Glaucoma</i>
Viral	
Congenital rubella syndrome (Rubella)	Angle dysgenesis, uveitis, lens-induced
Herpes keratouveitis (Herpes simplex)	Trabeculitis, open angle, angle closure
Herpes zoster ophthalmicus (Varicella zoster)	Trabeculitis, open angle, angle closure
Cytomegalovirus	Neovascular glaucoma*
Mumps	Uveitis, nonuveitic*
Influenza (Influenza A)	Acute angle closure*
Adenoviral keratoconjunctivitis (Adenovirus serotype 10)	Transient uveitic glaucoma
Bacterial	
Hansen's disease (<i>Mycobacterium leprae</i>)	Uveitis
Syphilis (<i>Treponema pallidum</i>)	Uveitis, late open angle, Late chronic angle closure Late acute angle closure
Protozoal	
Toxoplasmosis (<i>Toxoplasma gondii</i>)	Transient uveitic glaucoma
Parasitic	
Onchocerciasis (<i>Onchocerca volvulus</i>)	Uveitis
Toxocariasis (<i>Toxocara canis</i>)	Uveitis
Fungal	
Coccidioidomycosis (<i>Coccidioides immitis</i>)	Severe iridocyclitis, granulomatous TM obstruction

TM, trabecular meshwork; *, suspected mechanism.

TABLE 30-5 PHAKOMATOSES AND GLAUCOMA

<i>Disease</i>	<i>Mechanism</i>
Sturge-Weber syndrome (Encephalotrigeminal angiomas)	Immature angle development Elevated episcleral venous pressure Neovascularization of TM Premature aging of the TM
Klippel-Trenaunay-Weber	Anomalous angle development
Neurofibromatosis Type 1 (von Recklinghausen disease)	Neurofibromatous angle infiltration Angle-closure, nodular thickening of the ciliary body or choroid Angle-closure, fibrovascular membrane resembling neovascular glaucoma Immature anterior chamber angle development
Von-Hippel-Lindau syndrome (rare)	Rubeosis iridis Iridocyclitis
Nevus of Ota (Oculodermal melanocytosis)	Chronic open-angle glaucoma
Pigmentovascularis	Congenital glaucoma
Diffuse congenital hemangiomatosis	Immature iridocorneal development
Wyburn-Mason syndrome	Neovascular glaucoma
Tuberous sclerosis	Neovascular glaucoma

TM, trabecular meshwork.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome (encephalotrigeminal angiomas) (see also Chapter 23) is a dermatoo-oculoneuronal syndrome characterized by hamartomatous hemangiomas of the facial skin, ipsilateral diffuse cavernous hemangioma of the choroid, and ipsilateral leptomeningeal angioma (Fig. 30-4A–C). The cutaneous angioma causes the characteristic nevus flammeus or portwine stain in the distribution of the first, occasionally the second, and rarely all three branches of the trigeminal nerve. The nervous system involvement frequently causes seizures, hemispheric motor or sensory deficits, and mental retardation. This syndrome is rarely bilateral.⁶⁸

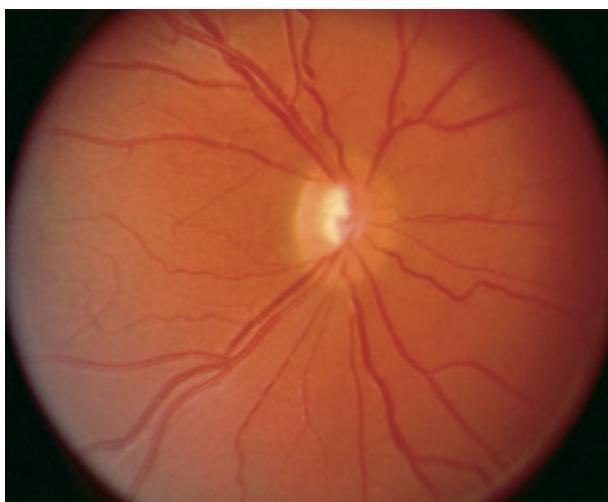
Glaucoma occurs in approximately one half of patients, ranging from 30 to 71%. Patients whose cutaneous angioma involve both upper and lower eyelids

and the ophthalmic and maxillary distributions of the trigeminal nerve are particularly at risk. The ipsilateral eye is frequently enlarged, and biomicroscopic examination reveals a dense conjunctival or episcleral vascular plexus ipsilateral to the cutaneous angioma.^{69–71}

The mechanism of glaucoma in Sturge-Weber syndrome is controversial and its treatment is difficult (Chapter 23). Although glaucoma is usually seen in infants, it may present later in life. In infants, histopathologic studies have demonstrated immature anterior chamber angle development similar to congenital glaucoma. Management of these cases follows the guidelines for congenital glaucoma, with goniotomy or trabeculotomy as a first choice. Other patients have open and normal anterior chamber angle structures. Here, the episcleral AV malformation is thought to increase IOP through elevated episcleral venous pressure.⁷²



A



B

FIGURE 30-4 (A) Nevus flammeus (portwine stain) and ipsilateral choroidal hemangioma in a child with Sturge-Weber syndrome. Note the “tomato ketchup” appearance of (B) the right fundus compared to (C) the normal left fundus.



C

Although medical therapy may be sufficient to control the form of glaucoma that occurs later in life, trabeculectomy, trabeculotomy, combined trabeculectomy-trabeculotomy and argon laser trabeculoplasty have also been advocated. Filtering surgery is frequently associated with intraoperative choroidal effusion or, occasionally, expulsive choroidal hemorrhage, for which many surgeons will perform a prophylactic posterior sclerotomy in conjunction with the filtration surgery.^{73,74}

KLIPPEL-TRENAUNAY-WEBER SYNDROME

Klippel-Trenaunay-Weber syndrome, characterized by cutaneous hemangiomas, varicose veins, and soft tissue and bony hypertrophy, shares features of vascular malformation with Sturge-Weber syndrome and may represent a variant of a similar disease process. Histopathologic study has demonstrated anomalous anterior chamber angle development akin to congenital glaucoma.⁷⁵

NEUROFIBROMATOSIS

Neurofibromatosis Type 1 (NF-1, peripheral NF, von Recklinghausen disease) is the most common phakomatosis with a frequency of 1:3500 to 4000 in the general population. This autosomal dominant disorder, localized to chromosome 17q11, is characterized by cutaneous café au lait

spots, axillary and inguinal freckling, Lisch nodules, cutaneous neurofibromas, optic nerve gliomas, and other solid neoplasms of the central nervous system (Fig. 30-5A-C). Lisch nodules are melanocytic hamartomas on the iris stroma and are a near constant finding in NF-1. Multiple small choroidal nevi may also be seen. Optic nerve gliomas are present in 10 to 15% of patients, and neurofibromas, which arise from Schwann cells, may involve the eyelids, conjunctiva, iris, ciliary body, and choroid.^{76,77}

Elevated IOP is more common in NF-1 when the eyelids are involved. Mechanisms of glaucoma include infiltration of the angle with neurofibromatous tissue, closure of the anterior chamber angle due to nodular thickening of the ciliary body or choroid, a fibrovascular membrane resembling neovascular glaucoma, and anomalous or immature anterior chamber angle development.⁷⁸

VON-HIPPEL-LINDAU SYNDROME

Von-Hippel-Lindau syndrome is an autosomal dominant multiorgan disorder linked to chromosome 3p25-26 characterized by retinal capillary hemangiomas, central nervous system hemangioblastomas (particularly of the cerebellum), solid and cystic hamartomas of visceral organs, and malignant neoplasms, which include renal cell carcinoma and pheochromocytoma. Affected individuals are at a substantial risk of early death. When glaucoma occurs in

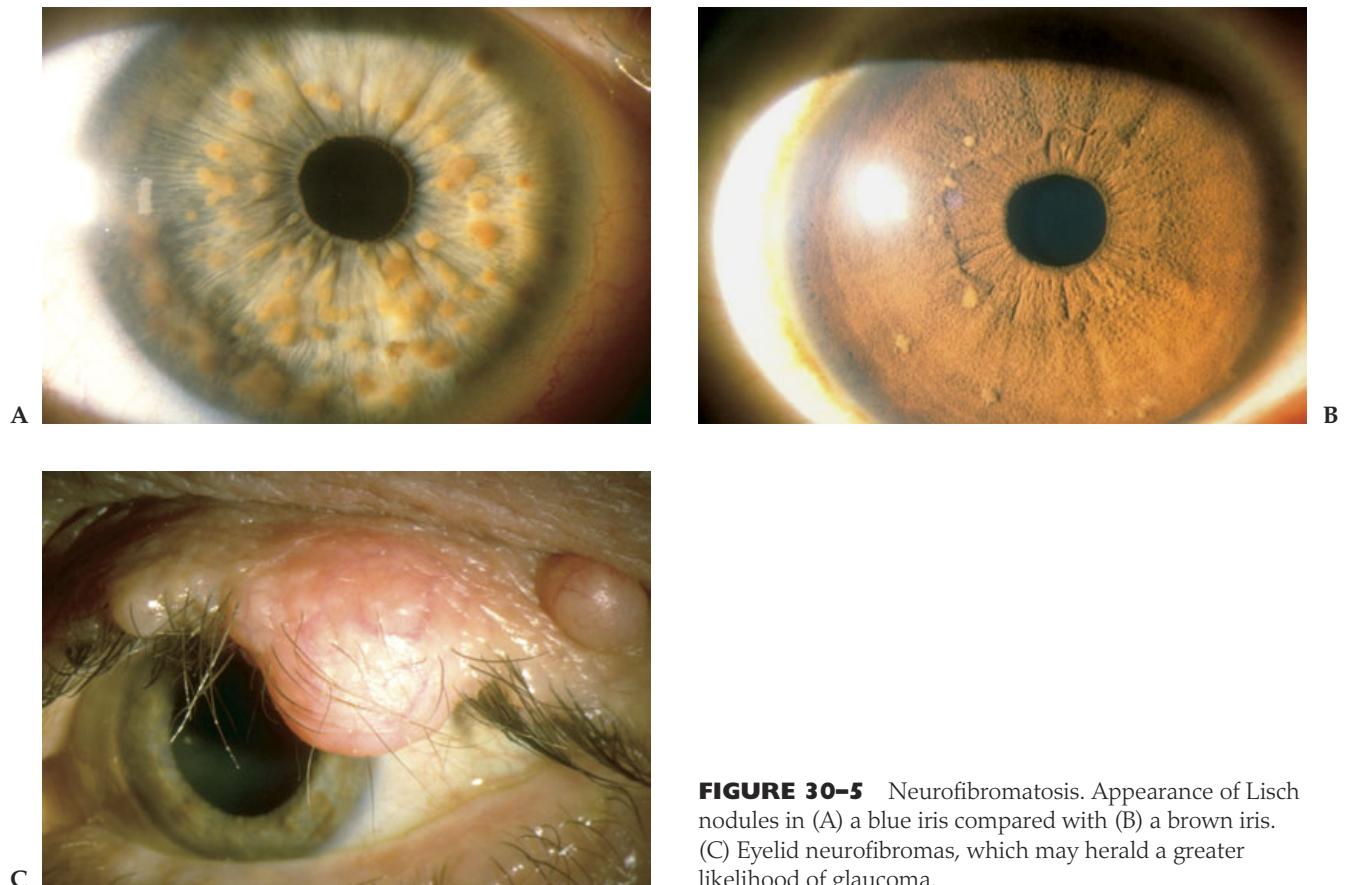


FIGURE 30-5 Neurofibromatosis. Appearance of Lisch nodules in (A) a blue iris compared with (B) a brown iris. (C) Eyelid neurofibromas, which may herald a greater likelihood of glaucoma.

these patients, it usually results from neovascular glaucoma or iridocyclitis following retinal detachment from untreated exudative capillary hemangiomas.⁷⁹

OCULODERMAL MELANOCYTOSIS

In oculodermal melanocytosis, nevus of Ota (Chapter 29), a unilateral, increased accumulation of melanocytes in the episclera and skin, occurs in the distribution of the trigeminal nerve, particularly in races with darker skin pigmentation (Fig. 30–6A,B). Ocular hypertension occurs in approximately 10% of patients, typically affecting the hyperpigmented eye. Although the anterior chamber appears clinically open, histopathologic studies have revealed a higher density of melanocytes in the trabecular meshwork. Management of glaucoma follows the guidelines for POAG.^{80–82}

PIGMENTOVASCULARIS

Pigmentovascularis represents the coincidence of neurocutaneous melanosis and encephalofacial angiomas. This neural crest disorder is found almost exclusively in Asians and, when it extensively involves the globe, predisposes the patient to congenital glaucoma, due in greater part to the vascular malformations. Patients with either oculodermal melanocytosis or nevus flammeus may develop ocular hypertension later in life and require lifelong monitoring.^{83,84}

DIFFUSE CONGENITAL HEMANGIOMATOSIS

Diffuse congenital hemangiomatosis is a condition characterized by multiple hemangiomas of the skin and mucous membranes. A single case of infantile glaucoma has been reported in a 7-month-old infant with this condition, apparently the result of immature iridocorneal development and angle vascularity.⁸⁵

WYBURN-MASON SYNDROME

The Wyburn-Mason syndrome is a sporadic disorder of retinal AV malformation, with approximately 25% incidence of coexisting intracranial AV communications. One half of patients have ipsilateral facial hemangiomas.



FIGURE 30-6 (A) Nevus of Ota, with excessive melanocytosis of the skin and (B) ipsilateral episclera.

Neovascular glaucoma has been reported in a 4-year-old girl who developed widespread retinal and choroidal ischemia.⁸⁶

TUBEROUS SCLEROSIS

Tuberous sclerosis (Bourneville disease) is an autosomal dominant, highly penetrant disorder with partial expressivity linked to the long arm of chromosome 9. Sporadic cases also exist. Brain and cutaneous involvement most frequently include the diagnostic ash leaf spots, angiofibromata ("adenoma sebaceum"), and seizures in a vast majority of patients. The most common ocular finding is retinal astrocytic hamartoma occurring in half of these patients. Rarely, these retinal hamartomas may cause exudative retinal detachment, which may lead to glaucoma from either a total retinal detachment or neovascularization.^{87,88}

METABOLIC DISEASES

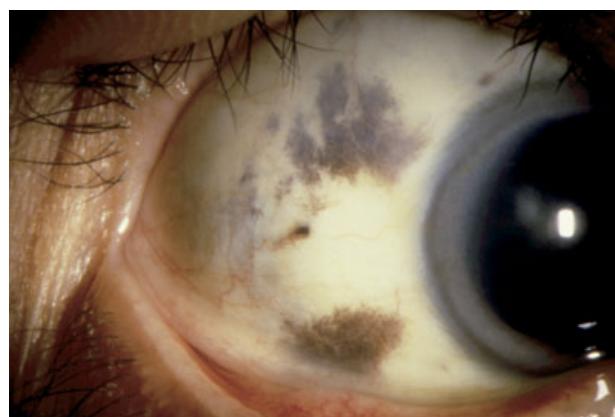
In congenital errors of metabolism, a gene defect causes an enzyme deficiency that leads to excessive systemic accumulation of metabolic products. Although many of these disorders affect the anterior segment of the eye, only a few occur with glaucoma (Table 30–6).

CYSTINOSIS

Cystinosis is a rare autosomal recessive disorder of amino acid metabolism. A defect in lysosomal cysteine transport causes cystine crystals to accumulate in lysosomes of the bone marrow, liver, spleen, lymphatics, and kidney. Cystine crystals can accumulate throughout the eye, and involvement of the iris can, on rare occasion, produce pupillary block.⁸⁹

MUCOPOLYSACCHAROIDOSSES

The mucopolysaccharidoses are a group of related conditions in which enzymatic defects in mucopolysaccharide metabolism cause progressive glycosaminoglycan accumulation in lysosomes. Corneal clouding and optic



B

TABLE 30-6 METABOLIC DISEASES AND GLAUCOMA

Disease Type	Mechanism
Disorders of amino acid metabolism	
Cystinosis	Pupillary-block glaucoma
Mucopolysaccharidoses	
Hurler (Type I-H)	Open angle (excess trabecular GAG deposition)*
Scheie (Type I-S)	Angle-closure, non-pupillary block (intermittent, chronic or acute, excess peripheral corneal GAG deposition)*
Hurler-Scheie (Type I-H/S)	
Hunter (Type II)	
Morquio (Type IV)	
Maroteaux-Lamy (Type VI)	
Peroxisomal disorders	
Zellweger syndrome	Angle maldevelopment

GAG, glycosaminoglycans. * These mechanisms apply to all mucopolysaccharidoses.

atrophy typically occur, with the former often hindering examination of the anterior chamber angle. Glaucoma may occur in Hurler (Type I-H),⁹⁰ Scheie (Type I-S), Hurler-Scheie (Type I-H/S),⁹¹ Hunter (Type II), Morquio (Type IV),⁹² and Maroteaux-Lamy (Type VI).⁹³ Secondary open-angle glaucoma can result from excessive glycosaminoglycan deposits obstructing the trabecular meshwork, although peripheral corneal thickening may produce intermittent, chronic, or acute angle-closure glaucoma without pupillary block.⁹⁰⁻⁹³

ZELLWEGER SYNDROME

Zellweger (cerebrohepatorenal) syndrome is an autosomal recessive peroxisomal disorder in which long-chain fatty acids are not metabolized, resulting in craniofacial dysmor-

phism, seizures, hypotonia, psychomotor retardation, hepatomegaly, and renal cysts. Ophthalmic manifestations include pigmentary retinopathy, optic atrophy, corneal clouding, cataract, and extinguished electroretinogram. Anterior chamber angle maldevelopment that results in a congenital form of glaucoma has been reported.⁹⁴

SYSTEMIC CONGENITAL ANOMALIES AND GLAUCOMA

Glaucoma may occur in several multisystem congenital syndromes and chromosomal anomalies. Most cases result from abnormal anterior chamber angle development resembling anterior segment dysgenesis or congenital glaucoma (Table 30-7).

TABLE 30-7 SYSTEMIC CONGENITAL ANOMALIES ASSOCIATED WITH ANTERIOR CHAMBER ANGLE MALDEVELOPMENT

Congenital Syndromes	Chromosomal Anomalies
Lowe (oculocerebrorenal) ^{95,96}	Trisomy 21 (Down's) ¹¹⁰
Rubenstein-Taybi (broad thumb) ^{97,98}	Trisomy D (13-15) ¹¹¹
Oculodentodigital dysplasia ⁹⁹	Trisomy 18 (Edward's) ¹¹²
Oculodento-osseous dysplasia ¹⁰⁰	Turner's (XO) ¹¹³
Cockayne (dwarfism and "birdlike" facies) ¹⁰¹	Partial trisomy 2q ¹¹⁴
CHARGE (coloboma, heart disease, atresia choanae, retarded growth, genital hypoplasia, ear anomalies, or deafness) ¹⁰²	Partial trisomy 3q ¹¹⁵
Diamond-Blackfan (erythroid hypoplasia, short stature, thumb anomalies, strabismus, hypertelorism, microphthalmos) ¹⁰³	Partial trisomy 16q ¹¹⁶
ter Haar (hypertelorism, heart defects, kyphoscoliosis, skeletal dysplasia, developmental delay) ¹⁰⁴	Combined trisomy 2q and monosomy 9p ¹¹⁷
GAPO (growth retardation, alopecia, pseudoanodontia, optic atrophy) ¹⁰⁵	Pericentric inversion of chromosome 11 ¹¹⁸
3C (craniocerebellocardiac dysplasia) ¹⁰⁶	Ring chromosome 6 ¹¹⁹
MEB (muscle-eye-brain disease) ¹⁰⁷	
SHORT (short stature, hyperextensibility of joints, hernia, ocular depression, Rieger anomaly, teething delay) ¹⁰⁸	
Kniest dysplasia ^{97,109}	

PEARL... Most congenital and chromosomal syndromes associated with glaucoma result from poor development of the anterior chamber angle.

Several systemic congenital syndromes that may cause glaucoma by a variety of other mechanisms are discussed in the following text.

STICKLER'S SYNDROME

Stickler's syndrome (Chapter 27) is an autosomal dominant progressive arthro-ophthalmopathy resulting in orofacial and skeletal abnormalities. Ocular manifestations include high myopia, cataracts, vitreoretinal degeneration, and retinal detachment. Open-angle, anterior segment dysgenesis and neovascular forms of glaucoma have all been reported.^{120,121}

MARFAN'S SYNDROME

The most common mechanism of glaucoma in Marfan's syndrome (see also Chapter 25) is pupillary block from dislocation of the crystalline lens.^{122,123} However, glaucoma may also result from abnormal development of the anterior chamber angle, resembling Axenfeld's anomaly.

WEILL-MARCHESANI SYNDROME

Weill-Marchesani (Chapter 25) is a syndrome of short stocky stature, brachydactyly, microspherophakia, lens ectopia, and glaucoma. Both autosomal recessive and dominant forms have been identified.^{124–126} Pupillary block angle closure by forward displacement of a small spherical lens from loose zonules or subluxation is the most common mechanism of glaucoma, and this may be exacerbated by miotics, which reduce zonule tone on the lens equator.¹²⁴

PRADER-WILLI SYNDROME

Prader-Willi is a condition of hypotonia, hypogonadism, obesity, mental retardation, oculocutaneous albinism, and ectropion uvea. Some patients may develop an open-angle form of glaucoma.^{127,128}

HALLERMAN-STREIFF SYNDROME

Hallerman-Streiff syndrome, a condition of micrognathia and dwarfism, is associated with cataracts and microphthalmos. Glaucoma has been reported secondary to resorption of lens material or in association with aniridia.^{99,129}

RETINOPATHY OF PREMATURITY

Glaucoma may occur in infants, children, and adults with retinopathy of prematurity (ROP) (see also Chapter 27) and

in an estimated 20 to 30% of patients with advanced ROP.^{130–134}

In infants and children with advanced ROP, secondary angle closure results from anterior displacement of the lens–iris diaphragm by a contracting retro-lental membrane,^{135–137} ciliary block,¹³⁸ pupillary block,¹³³ and uveitic peripheral anterior synechiae.¹³⁹ Goniodysgenesis may also contribute to glaucoma because gonioscopy of children with advanced ROP reveals many developmental angle abnormalities.^{140–141} Finally, vitrectomy for advanced ROP can be complicated by neovascular glaucoma.

Adults with ROP may also develop angle-closure glaucoma, most likely through ciliary block, pupillary block, and neovascular glaucoma. The shallower anterior chambers and larger crystalline lenses in these patients probably account for their myopia and proclivity to develop phacomorphic pupillary block. Laser iridotomy or surgical iridectomy may prevent synechial angle closure, whereas cataract extraction is indicated for patients with intumescent lenses.¹⁴² Less commonly, adults with ROP can develop neovascular angle closure.

PRIMARY FAMILIAL AMYLOIDOSIS

The primary familial amyloidoses are a group of autosomal dominant disorders with widespread generalized amyloid deposition, causing weakness, peripheral neuropathy, and gastrointestinal, cardiovascular, renal, and endocrine abnormalities. Ocular involvement includes accumulation of potentially vision-limiting cotton-like amyloid vitreous opacities, eyelid abnormalities, extraocular muscle weakness, proptosis, conjunctival microaneurysms, internal ophthalmoplegia, irregular pupillary margin, anisocoria, and retinal perivasculitis.¹⁴³

In these rare diseases, up to one fourth of patients might develop bilateral, severe open-angle glaucoma,¹⁴⁴ with iris transillumination defects, pigmented trabecular meshwork, and corneal endothelium.^{144,145} Amyloid deposition and degenerative changes in the trabecular meshwork may obstruct aqueous outflow.^{143,144,146,147}

An open-angle glaucoma may also occur in Type II (Finnish-variant) familial amyloidosis, in which patients have cranial neuropathy and lattice corneal dystrophy.¹⁴⁸

RADIOTHERAPY

IONIZING RADIATION

Various mechanisms have been suggested for the development of glaucoma following irradiation for intraocular tumors or regional head and neck tumors. Of these, neovascular glaucoma is well established. Ion-

izing radiation, which directly damages tumor cell DNA to produce cell death, can also cause choroidal and retinal vascular fibrosis and closure, resulting in ischemia and neovascularization.¹⁴⁹ Other proposed mechanisms include iridocyclitis, hyphema, peripheral anterior synechiae, scleral necrosis, and pigment dispersion.^{150,151} Elevated episcleral venous pressure, direct obliteration of the outflow channels,^{150,151} and hemolytic glaucoma from persistent vitreous hemorrhage¹⁵² have also been suggested.

Approximately 29 to 36% of eyes treated with charged-particle external beam radiation can develop neovascular glaucoma.^{153–157} In contrast, the incidence is lower (1 to 31%) following episcleral plaque brachytherapy.^{158–160} Here, the radiation source is sutured to the episclera over the base of the tumor. This limits radiation exposure the anterior segment to compared with charged particle external beam therapy, where 70% of the dose to the tumor reaches the anterior segment.¹⁵² Large intraocular tumors more often produce neovascular glaucoma in irradiated eyes because they are more likely to induce retinal hypoxia and be associated with concurrent retinal detachment.¹⁶¹

Because the effects and complications of irradiation are often delayed, these eyes require long-term monitoring. In eyes with heavy irradiation, cataract surgery may accelerate the development of neovascular glaucoma,¹⁶² and perioperative photoablation of the ischemic retina may be indicated.

ATHERMOTHERAPY

Hyperthermia is a nonionizing treatment for intraocular tumors used either alone or with brachytherapy or chemotherapy.^{163–165} Although this technique may enhance the effect and safety of radiotherapy, thermotherapy alone can also cause neovascular glaucoma.¹⁶⁵

DRUGS CAUSING GLAUCOMA

CORTICOSTEROIDS

In susceptible individuals taking corticosteroids reduced trabecular outflow and increases in IOP produce clinical features resembling POAG (Chapter 18). Although glaucoma most commonly results from topical administration of ophthalmic preparations, it may also occur with periocular, oral, or intravenous administration.^{166–168} Even prolonged administration of inhaled glucocorticoids and chronic facial application of potent corticosteroids can increase the risk of ocular hypertension or open-angle glaucoma.^{169–171} Treatment generally consists of discontinuing the offending agent, if possible, and medical and surgical intervention, if necessary.

PEARL... Although steroid-induced glaucoma most commonly occurs with topical ophthalmic eye drop administration, it may also result from periocular injections and oral, intravenous, inhaled, or dermatologic facial application of corticosteroids.

NONSTEROIDAL DRUGS

Systemic administration of certain nonsteroidal drugs may precipitate angle-closure glaucoma. Medications with anticholinergic or sympathomimetic effects can dilate pupils and precipitate angle-closure glaucoma in susceptible individuals (Table 30-8). Other drugs may

TABLE 30-8 DRUGS REPORTED TO CAUSE ANGLE-CLOSURE GLAUCOMA^{172,173}

Anticholinergic pupillary dilation

Antihistamines	Ethanolamine Orphenadrine (Norgesic)
Antiparkinsonian agents	Trihexyphenidyl HCl (Artane)
Antidepressants:	
Tricyclics	Amitriptyline (Elavil, Amitril) Imipramine (Tofranil) Clomipramine (Anafranil) ¹⁷⁴ Fluoxetine (Prozac)
Selective serotonin reuptake inhibitors	
Atypical agents	Paroxetine (Paxil) ^{175,176}
Monoamine oxidase inhibitors	Mianserin HCl (Bolvidon) Phenelzine sulfate (Nardil) Tranylcypromine (Parnate)
Antispasmodic agents	Propantheline bromide (Pro-Banthine) Dicyclomine HCl (Bentyl)
Antipsychotics	
Phenothiazines	Perphenazine (Trilafon), Fluphenazine decanoate (Prolixin)
Inhaled agents	Ipratropium
Mydriatics:	Cyclopentolate Tropicamide Atropine Homatropine Scopolamine

Sympathomimetic pupillary dilation

Sympathomimetics	Epinephrine Ephedrine Phenylephrine Hydroxyamphetamine Cocaine
------------------	--

Forward lens shift or lens swelling, phacomorphic angle closure, or anterior rotation of ciliary body

	Acetazolamide (Diaurox) Sulfanilamide Quinine Topiramate (Topamax)
--	---

TABLE 30-9 DRUGS REPORTED TO AGGRAVATE OPEN-ANGLE GLAUCOMA

Mydriatics	Cyclopentolate, Tropicamide, Atropine, Homatropine, Scopolamine
Sympathomimetics*	Epinephrine, Phenylephrine, Amphetamine, Hydroxyamphetamine
Inhaled agents	Salbutamol

*Mechanisms unclear.

cause angle closure by encouraging swelling or forward movement of the lens. Prevention of glaucoma from nonsteroidal drugs lies in identifying patients at risk by determining their medication regimen, history of glaucoma, and potential for anterior chamber angle occlusion. Nonsteroidal drugs are rarely contraindicated in patients with open-angle glaucoma or patent iridotomies.^{172,173}

PEARL... Patients with occludable angles who have to take medications with anticholinergic or sympathomimetic effects may require prophylactic iridotomy to prevent acute angle-closure glaucoma.

Mydriatic agents that act through anticholinergic mechanisms are the nonsteroidal agents most likely to exacerbate open-angle glaucoma (Table 30-9). Presumably, these agents diminish ciliary muscle tone and further reduce outflow facility through an already compromised trabecular meshwork. Because of this, practitioners should defer using these agents to dilate patients with already highly elevated IOP and advanced optic nerve damage until after the pressure is better controlled.

INTRA-ARTERIAL CHEMOTHERAPY

Elevated IOP may follow intracarotid administration of chemotherapeutic agents to treat patients with central nervous system malignancies. Intra-arterial chemotherapy, particularly when delivered inferior to the ophthalmic artery, can produce severe orbital inflammation and several ocular complications. Orbital congestion and uveal effusion can both contribute to elevated IOP in this setting.^{177,178}

TERATOGENS

Teratogenic effects of alcohol^{179,180} and thalidomide¹⁸¹ have been associated with maldevelopment of anterior chamber angle structures, resulting in a congenital form of glaucoma.¹⁷⁹⁻¹⁸¹

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SECTION V

MEDICAL THERAPY OF GLAUCOMA

PRINCIPLES OF OCULAR MEDICATIONS

Reay H. Brown, M.D., and Gary D. Novack, Ph.D.

The vast majority of glaucoma is treated with eyedrops, and successful glaucoma management requires a comprehensive understanding of topical ocular therapy. The conjunctival cul-de-sac is a unique pharmacokinetic environment and provides many challenges to effective topical therapy. The principles reviewed here can be applied to subsequent chapters dealing with each specific drug class.

In selecting the optimal medication, practitioners should consider the properties of drugs (e.g., potency and efficacy), and the optimal dosing formulation (e.g., solution, suspension, gel). The physician should also confirm that the patient receives education about the proper instillation of medications, and the importance of adhering to the prescribed regimen. Finally, with continuing changes in health care management and pharmaceutical developments, issues of generic versus branded medication are having an increasing impact on chronic, topical glaucoma therapy.

PROPERTIES OF DRUGS

The properties of drugs include efficacy, potency, and therapeutic index. Efficacy measures the magnitude of a drug's therapeutic action [e.g., percentage of patients achieving a clinically significant reduction in intraocular pressure (IOP)]. Potency (or concentration, in the case of eyedrops) is a measure of the quantity of drug required to produce a given effect. For example, timolol used at the 0.25 and 0.5% strength is severalfold more potent than pilocarpine used at the 2 to 4% strength. However, the two agents are similar in ocular hypotensive efficacy.¹

Therapeutic index is the ratio of drug efficacy to the magnitude of adverse side effects. For example, fluorometholone is less likely to cause steroid-induced glaucoma than dexamethasone, but its anti-inflammatory activity is also less potent.² Thus the two agents have a similar therapeutic index.

Other drug properties include receptor selectivity, corneal penetration, and protein/melanin binding. Receptor selectivity of action compares the potency at different receptors. For example, timolol maleate has a similar potency at both beta₁- and beta₂-adrenoceptors. In contrast, betaxolol is 100 times more potent at the beta₁-adrenoceptor than at the beta₂-adrenoceptor.³

OCULAR PHARMACOKINETICS

Pharmacokinetics is the study of the rate of processes that govern absorption, distribution, metabolism, and excretion of a medication.⁴ Figure 31–1 presents a schematic of these processes in the eye.

ABSORPTION OF MEDICATIONS FROM THE CONJUNCTIVAL CUL-DE-SAC

The precorneal tear film normally contains 7 to 10 µL.⁵ After instillation of an eyedrop, the tear film can momentarily hold up to 30 µL before the patient blinks. Blinking causes the majority of the drop to spill out onto the cheek while the remaining portion is pumped into the lacrimal system and becomes available for systemic absorption. In addition, the drop administration provokes reflex tearing, which further dilutes the drug.

The average size of a commercial eyedrop is 39.0 µL, with a range of 25.1 to 56.4 µL.⁶ With large losses of medications occurring from spillage and lacrimal drainage, it is not surprising that only 1 to 7% of an instilled dose penetrates the cornea.⁷

CORNEAL PENETRATION

Three layers of the cornea act as barriers to drug permeability: the epithelium, the stroma, and the endothelium. The lipid-rich epithelium is the strongest barrier. Thus,

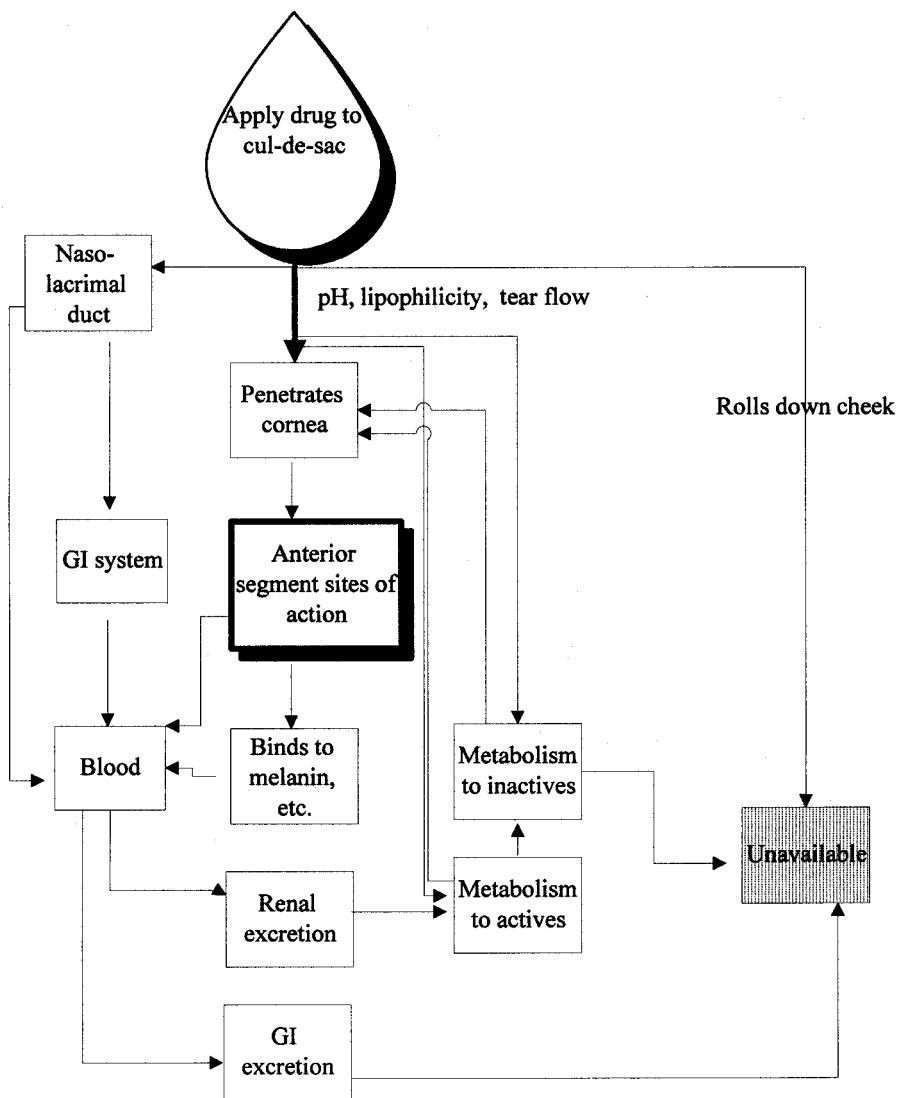


FIGURE 31-1 Schematic diagram of factors influencing the absorption, distribution, metabolism, and excretion of topically applied drugs.

molecules with high lipid solubility will have better corneal penetration. The stroma is 78% water and is passed most easily by hydrophilic drugs. Because the lipophilic endothelium is only one cell layer thick, it is a much weaker barrier than the epithelium. Some molecules, such as apraclonidine, have a low lipid solubility and do not penetrate the cornea well. However, applied in higher concentrations than their lipophilic analogs, they can still enter the aqueous humor through the conjunctiva and sclera.⁸

DISTRIBUTION, METABOLISM, AND ELIMINATION OF DRUGS WITHIN THE EYE

Medication entering the anterior chamber is immediately diluted as it mixes with aqueous from the anterior and posterior chambers. Elimination of the drug occurs mainly through turnover of aqueous, which drains out via the trabecular meshwork. Medications also may be bound to aqueous proteins and melanin in the iris and ciliary body. Melanin binding may account for the

reduced effect of timolol in persons with darker irides⁹ and may explain why timolol remains active long after the treatment is stopped.¹⁰

Esterases are common in the eye and are known to activate pro-drugs (e.g., the conversion of dipivefrin to epinephrine)¹¹ and inactivate soft drugs (i.e., drugs that are active, but metabolized in situ to inactive agents, such as loteprednol etabonate to PJ-91).¹² The cornea also contains hydroxylases, which can convert levobunolol to dihydronolol, its active metabolite,¹³ and phenylephrine oxazolidine (which is inactive) to phenylephrine.¹⁴ Furthermore, the eye contains monoamine oxidases, which contribute to the catabolism of epinephrine.¹⁵ Although ocular cytochrome p450 levels are highest in the ciliary epithelium and retinal pigment epithelium, they are still severalfold lower than in tissues such as liver and lung.¹⁵⁻¹⁷ Thus this enzyme system, which is very important in the metabolism of drugs taken by oral and intravenous routes, does not significantly affect the bioavailability of topically applied ocular medications.

SYSTEMIC ABSORPTION

Shell estimated that as much as 80% of an eyedrop volume drains through the nasolacrimal system, where it is available for systemic absorption.¹⁸ The frequency and variety of systemic adverse side effects associated with topical beta-adrenoceptor antagonists, and other medications, has increased our awareness of the dangers of systemically absorbed eyedrops. Both 5 minutes of nasolacrimal occlusion (NLO) and eyelid closure have been shown to reduce the systemic absorption of timolol by 60%.¹⁹ NLO itself may encourage eyelid closure. This method is both practical and involves no out-of-pocket cost for either the patient or the physician.²⁰

PEARL... One minute of eyelid closure following an eyedrop is a very practical, effective, and inexpensive way to reduce systemic drug absorption.

DOSAGE FORMS OF TOPICAL GLAUCOMA MEDICATIONS

Topical glaucoma medications can be formulated as aqueous solutions, suspensions, ointments, inserts, emulsions, and gels. Each formulation also contains inactive ingredients (excipients) that adjust pH, tonicity, and viscosity. In addition, all dosage forms designed for multidose administration must reduce the risk of contamination, through either preservatives or special containers. For all topical medications, the formulation, along with its additives, can profoundly affect ocular penetration, comfort, and efficacy (Table 31-1).

Drug delivery systems are designed to increase ocular absorption in a convenient manner while minimizing local and systemic side effects. The large variety of drug forms speaks eloquently to the difficulty of achieving these goals.

TABLE 31-1 PROPERTIES OF TOPICAL MEDICATIONS THAT AFFECT DRUG EFFICACY

Component/Formulation	Effect
Excipients	
pH (Ionization state)	Comfort and corneal penetration
Tonicity	Comfort
Viscosity	Increased corneal contact time and absorption
Preservatives	Antimicrobial; increased corneal penetration; contributes to allergic response
Aqueous solutions	Limited corneal contact and ocular penetration
Suspensions	Drugs with limited water solubility; need resuspension prior to use
Ointments	Prolonged corneal contact
Gels	Prolonged corneal contact

EXCIPIENTS

The pH of a formulation affects comfort, corneal penetration, and, ultimately, ocular absorption. Most topical medications exist in both ionized and nonionized forms. The nonionized form penetrates the lipophilic cornea more easily. For instance, changes in pH can increase ocular penetration of topical carbonic anhydrase inhibitors five- to sixfold.²¹

Active drug, preservative, and vehicle all affect the tonicity of ocular medications, and the eye can tolerate wide ranges of tonicity without irritation.²² By definition, an isotonic solution has the tonicity of 0.9% saline, or 290 mOsm,²³ and most commercial eyedrops (with the exception of some artificial tear formulations) are within the range of isotonicity (e.g., 260 to 320 mOsm). Agents that increase viscosity, such as various forms of methylcellulose, polycarbophil, and polyvinyl alcohol, may improve ocular absorption by reducing losses from drainage through the nasolacrimal duct and increasing corneal contact time. A vehicle containing polycarbophil has been shown to improve the duration of action for fluorometholone, a topical corticosteroid.²⁴

Preservatives, of which benzalkonium chloride is the most common, are added to all multidose formulations to minimize microbial contamination. In addition to their antimicrobial activity, preservatives may also increase ocular absorption by enhancing corneal penetration and can contribute significantly to ocular allergies.²⁵ In 2001, a chloro-oxy compound, Purite, was introduced in place of benzalkonium chloride in a new formulation of brimonidine (Alphagan-P) to help diminish allergic side effects.^{25a}

Unfortunately, the presence of these antimicrobial agents does not protect all dropper tips from contamination.²⁶ Several novel systems have been developed for providing multidose convenience without the perceived toxicity of preservatives. For example, Ursapharm (Saarbrucken, Germany) has a system called Comod, which allows only unidirectional airflow, preventing the introduction of ambient, and possibly contaminated air, into the bottle.²⁷

AQUEOUS SOLUTIONS

Most topical glaucoma medications are formulated as aqueous solutions. This dosage form is probably the least expensive and easiest to apply, and generally does not cause blurred vision. However, aqueous solutions drain rapidly into the lacrimal system, which limits corneal contact time and ocular penetration.

SUSPENSIONS

Drugs with limited water solubility can be suspended as solid particles in a liquid vehicle and applied as an eyedrop. Prednisolone acetate and other topical corticosteroids are some of the most commonly used suspensions, and ocular

absorption improves with decreased particle size.²⁸ However, the liquid must be shaken before each dose to resuspend the particles. Incomplete shaking and resuspension constitutes another way in which poor treatment adherence reduces drug delivery and efficacy.

OINTMENTS

Ointment formulations are commonly used for antibiotics and corticosteroids, and they improve ocular absorption through prolonged retention of drug in the cul-de-sac.²⁹ Although blurred vision generally limits patient acceptance of ointments for chronic glaucoma therapy, this can be minimized by having the patient use the ointment at bedtime.

GELS

Gels that form after contact with the ocular surface constitute *in situ*, gel-forming systems. When these medications are given as an aqueous solution, factors in the conjunctival cul-de-sac, such as temperature, pH, or the ionic milieu, trigger formation of the gel. Gels have proved useful in prolonging the duration of action of pilocarpine.^{30,31} Examples of pilocarpine gel formulations include Piloplex (an aqueous dispersion in a gel of lauryl methacrylate and acrylic acid),^{32,33} Pilopine HS (a gel formulated with Carbopol, also known as carbomer, a high-molecular-weight, cross-linked polymer of acrylic acid),³⁴ and PilaSite (a gel-forming suspension composed of pilocarpine/polycarbophil).³⁵

Timolol has now been formulated in Gelrite, a polysaccharide gellan gum in which gel formation is triggered by the presence of sodium ions in the tears. In chronic treatment, once-daily use of timolol in this gel product is equivalent to twice-daily use of timolol in solution.³⁶ For example, an open label study has shown the efficacy of a new timolol formulation dissolved in a polymer whose viscosity is temperature-dependent (WP-934), with minimal ocular problems.³⁷

OCULAR INSERTS

Numerous devices have been developed to enhance delivery of ocular medications. The Ocusert (no longer commercially available), a membrane ring applied underneath a patient's eyelid, and provides a continuous delivery of pilocarpine. The zero-order kinetics allow a much smaller total dose of pilocarpine to achieve IOP reduction equivalent to that of conventional pilocarpine eyedrops.^{38,39} In addition to avoiding frequent drop administration, the low, continuous dose of pilocarpine may minimize both the magnitude and the range of miosis and induced myopia, important side effects that reduce adherence to pilocarpine drop therapy.⁴⁰ Other devices, such as ophthalmic rods and paper strips, have been investigated for glaucoma treatment, but are not commercially available.^{41–43}

EYEDROPS: PRACTICAL CONSIDERATIONS

DROP SIZE

Pharmacokinetic studies have shown that maximal tear-film concentration is achieved with a 20 µL drop.⁴⁴ Delivering the same amount of drug in a smaller drop volume can increase the therapeutic index; this has been demonstrated with phenylephrine.⁴⁵

This increased therapeutic index occurs because smaller drop volumes induce less reflex tearing, reduce the volume of drug available for systemic absorption, and decrease waste from spillage. Despite these considerations, the concept of reduced drop size has not been extensively applied to ophthalmic medications.

HOW TO TAKE A DROP

Successful topical glaucoma therapy depends on proper eyedrop administration technique, another link in the treatment adherence chain. The patient must not only take the medication at the appropriate time but must also instill the drop properly. Self-administration may be difficult in patients with arthritis, movement disorders, and dementia.

There are many ways to instill an eyedrop, and every good technique starts with washing the hands. In one technique, the patient gently pulls down the lower lid with the index finger of the hand not holding the dropper. One drop is then placed in the inferior cul-de-sac without touching the dropper tip to the conjunctiva, lashes, or skin. An alternative technique uses the thumb and index finger to create a pouch out of the inferior cul-de-sac (Fig. 31–2A). Avoiding contamination requires that the drop falls freely from the tip into the cul-de-sac. This may be easier to achieve if another person gives the drop because self-administration is generally difficult for the elderly glaucoma patient, who may have limited dexterity and vision.

Patients who administer their own drops may find it easier to tilt the head back and sight the dropper tip directly above the eye before instilling the drop. Resting the “dropper hand” on the hand pulling the lid may also help the patient apply the drop accurately and consistently. Looking downward after the drop contacts the eye increases space in the inferior cul-de-sac⁴⁶ and may limit blinking out the medication.

Another method that may work for both children and adults is to have the patient lie down, close the eye, and place the drop in the well that is located just nasal to the inner canthus. By tilting the head slightly to the left (for the right eye) or to the right (for the left eye), the drop will roll into the eye when the eyelids are opened.

After instilling the drop, the patient should close the eye for at least 1 minute. Simple eyelid closure can



FIGURE 31-2 (A) One technique for eyedrop instillation uses the thumb and forefinger to pull the lower eyelid out, creating a pouch for the drop out of the lower cul-de-sac. (B) Immediately following any eyedrop, the patient should close the eyelid and occlude the punctum for at least 1 minute. This limits access of the drop to the nasolacrimal duct and reminds the patient not to blink.

substantially reduce systemic absorption of topical medications.¹⁹ Although 5 minutes of eyelid closure may be more effective, the 1-minute recommendation is a good compromise to increase treatment adherence. Nasolacrimal occlusion (NLO) can also be effective in reducing systemic absorption through the lacrimal system¹⁹ and helps remind the patient to keep the eye closed (Fig. 31-2B). NLO, however, is more difficult to perform successfully, requires more instruction, and in itself may not reduce systemic absorption significantly beyond the reduction achieved by eyelid closure alone.

Do not underestimate the challenge of proper eyedrop instillation. Prescribing practitioners should develop their own method for taking eyedrops so they are better equipped to help patients develop their own technique. Patients should be carefully instructed in eyedrop instillation by the doctor or a technician and should be periodically observed administering their drops to confirm that their technique is satisfactory. Some patients find that refrigerating the bottle provides feedback with the feeling of the cold drop when it is correctly instilled. Studies observing patients taking eyedrops have demonstrated problems with wasting medication, contamination of dropper tips, and even complete failure to place the drop in the eye.^{47,48}

If more than one kind of drop is required at a particular time, the order of instillation may depend upon the pharmacology of each agent. For example, if the patient is using both an adrenergic agonist (e.g., brimonidine) and an adrenergic antagonist (e.g., timolol), then pharmacology suggests that the agonist should precede the antagonist.⁴⁹ The interval between the two instillations should be 5 minutes or greater, based upon studies in rabbits with radio-labeled drugs.⁵⁰ This delay prevents the additional drop from diluting and washing out the first drop before it gets absorbed. Ointments should be placed in the eye last.

PEARL... Patients should instill agonists before antagonists when multiple drugs are applied at the same time.

The development of new classes of glaucoma medications has increased the complexity of the treatment plan for some patients. Patients can now potentially use as many as five medications to treat glaucoma: a beta-adrenoceptor antagonist, an alpha-adrenergic agonist, prostaglandin analog, carbonic anhydrase inhibitor, and a miotic. It is helpful to write out the medications and dosage schedule at each visit. The increasing variety of available medications has required a dramatic expansion of a typical preprinted medication schedule, as illustrated in Figure 31-3.

COST OF GLAUCOMA MEDICATIONS

The cost of glaucoma medications is a major public health concern. Factors influencing cost include shelf price, drop size, doses per day, and average amount wasted per instillation. Despite their relative equivalence in efficacy, the cost of beta-adrenoceptor antagonist eyedrops varies widely.⁵¹

GENERICs

The Food and Drug Administration (FDA) governs the approval process for ophthalmic medications. However, the FDA does not currently require new generic medications to use clinical tests to prove equivalent efficacy with the parent medication or reference-listed drug (RLD). Thus, generic products are considered therapeutically equivalent if they contain the same active ingredient and are identical in strength, concentration, dosage form, and route of administration. Other ingredients, such as

		BREAKFAST	LUNCH	DINNER	BEDTIME
YELLOW CAP	Timoptic XE Timoptic 0.5% Timolol 0.5% Betagan 0.5% Ocupress Betimol				
PURPLE CAP	Alphagan-P Propine				
BLUE CAP	Betoptic-S Timolol 0.25%				
ORANGE CAP	Trusopt Azopt				
BLUE-GREEN CAP	Xalatan Travatan Lumigan Rescula				
GREEN CAP	Pilocarpine Phos. Iodide				
RED CAP	Atropine Cyclogyl				
WHITE CAP	Cosopt Pred Forte Prednisolone acetate				
TABLET, or CAPSULE	Diamox Neptazane				

FIGURE 31-3 A medication dosing sheet for glaucoma patients.

preservatives, pH adjusters, antioxidants, viscosity agents, and buffers, may be different without triggering a requirement for clinical testing.⁵²

Questions have been raised regarding the efficacy of generic topical corticosteroid suspensions compared with the branded products. In some cases, the size of the suspended prednisolone acetate particles in the brand products may be smaller than those in the generics. This may improve drug delivery because smaller particles may resuspend more easily with less shaking of the bottle. For example, one generic prednisolone acetate reached only 10% of its maximum concentration after the bottle was shaken five times as compared with 47% for the brand name product,⁵³ resulting in less available medication. In addition, the larger particles in generic prednisolone acetate can settle out and clog the dropper tip.⁵⁴

The absence of clinical testing of generics is a great concern in treating a chronic disease such as glaucoma. With an acute clinical problem, such as an infection, the efficacy of a generic can be assessed relatively quickly by the clinical response.⁵² However, the efficacy in treating chronic glaucoma is much more elusive. Small changes

in comfort due to changes in "inactive" ingredients can greatly affect treatment adherence and efficacy. But the lack of efficacy, or the lack of treatment adherence, may not be evident for years and may be impossible to attribute to problems with the medication because so many other factors intervene in glaucoma.

As generic substitution continues to increase, patients will frequently ask their doctors whether the generic product is acceptable. It is difficult to give unqualified endorsement to generic substitution in the absence of objective clinical data proving therapeutic equivalence with the RLD. However, because the generic product is often cheaper and simpler to obtain in a managed care setting, opposing the use of generics may impose financial difficulties for the patient. Another problem is that pharmacists are not required to notify the physician that they have made a generic substitution.⁵² Therefore, the physician may not realize that the patient did not receive the prescribed medication. At each clinic visit the practitioner or staff should routinely question the patient about the use of generic medications. If the clinical status changes, such as loss of pressure control, and the patient has changed to a generic medication, the physician

should re-prescribe the brand name product, with instructions to "dispense as written."

CONTROVERSY

Most generic ophthalmic solutions are approved by the FDA without evaluation of safety and efficacy in humans.

TREATMENT ADHERENCE

Treatment adherence (patient compliance) is a critical component of glaucoma treatment. In general, adherence rates decrease if a disease is asymptomatic, the dosing regimen is complex, and there are undesirable side effects from the drug.⁵⁵ Thus, glaucoma therapy is at great risk for poor treatment adherence. Treatment adherence rates for number of doses taken among glaucoma patients range from 76 to 84%. In one study, 6% took fewer than one quarter and 15% took fewer than one half of their prescribed drops.^{56,57}

Doctors have limited ability to determine which patients are noncompliant,⁵⁸ and treatment adherence can be particularly difficult to assess in glaucoma because a single drop taken shortly before the appointment may give a false impression of pressure control. Patterns of nonadherence include missed doses, inappropriately timed doses, and long intervals between dosing. Typically one sixth of patients have substantial nonadherence patterns. Drugs with short half-lives are less "forgiving" of nonadherence, resulting in longer periods without adequate tissue drug levels.⁵⁹ Poor adherence probably contributes to the well-documented observation that many glaucoma patients suffer continuing visual loss despite apparently well-controlled IOP.^{60–62} In glaucoma therapy, it is difficult to distinguish between nonresponders and patients who are nonadherent.⁶³ This increases the importance of monitoring the optic nerve and visual fields for signs of continuing damage.

PEARL... Patients and doctors both tend to overestimate treatment adherence. Always emphasize and question patients regarding their drops and how they use them.

Many factors can improve treatment adherence. These include careful patient instructions, a good doctor–patient relationship, and a better understanding of the disease process and the need for treatment by the patient. It is also helpful to simplify the dosing schedule, use medications with the fewest side effects, and discuss at each visit the importance of using the medications as prescribed.

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ADRENERGIC AGONISTS

Janet B. Serle, M.D., and Anthony C. Castelbuono, M.D.

Adrenergic agonists are potent ocular hypotensive agents that vary substantially in their utility for treating glaucoma. They include the nonselective alpha₁-/alpha₂/beta-adrenergic agents epinephrine and dipivefrin, and the differentially selective alpha₂-adrenergic agents clonidine, apraclonidine, and brimonidine.

Nonselective sympathomimetic agents were a mainstay in glaucoma management for many decades. However, high rates of ocular irritation and tachyphylaxis have relegated them to fourth-line options for chronic management in the United States. The alpha₂-selective adrenergic agonists appear to represent a considerable improvement over these older compounds, and the most recent entrant, brimonidine, has gained wide acceptance in long-term intraocular pressure (IOP) treatment for glaucoma.

NONSELECTIVE ADRENERGIC AGONISTS

BACKGROUND

Epinephrine was first used to treat glaucoma over a century ago.¹ Hamburger popularized adrenaline in the 1920s by the introduction of two synthetic agents, glaucosan and levo-glaucosan.^{2,3} Unfortunately, indiscriminate use resulted in variable changes in IOP, and undesired side effects caused the drug to fall into disrepute. It was reintroduced and widely accepted for the treatment of open-angle glaucoma in the early 1950s,⁴ and nonselective adrenergic agonists remained an important treatment for glaucoma. This was due, in part, to the development of the pro-drug, dipivalyl epinephrine. The pro-drug's advantage, decreased side effects through decreased administered dose, materialized as predicted when it was first synthesized and released in the 1970s.

SPECIAL CONSIDERATION

Pro-drugs are agents that are transformed into their pharmacologically active form in the body, following administration.

MECHANISM OF ACTION

The adrenal medullary hormone, epinephrine, is the systemic analog of the neurotransmitter, norepinephrine (Figure 32-1A). These are nonselective agonists for all the subtypes of both alpha- and beta-adrenergic receptors. Studies indicate that epinephrine stimulates the beta-receptor of the ciliary body,⁵ producing an early increase in aqueous flow. However, the predominant effect of epinephrine results from alpha₂-receptor-mediated vasoconstriction in

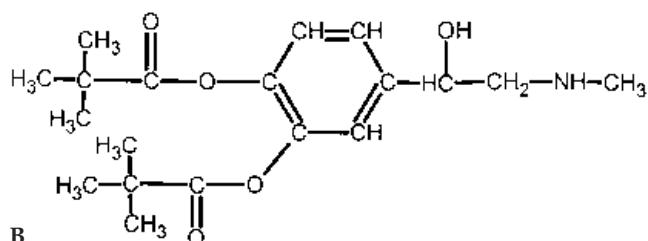
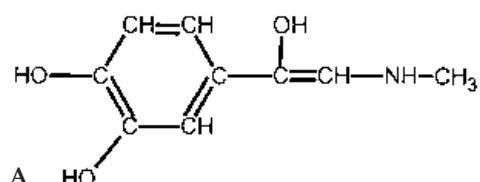


FIGURE 32-1 Nonselective adrenergic agonists.
(A) Epinephrine. (B) Dipivalylnepinephrine.

the ciliary body, which decreases aqueous production. In addition, experimental models have implicated an increase in outflow facility, both via beta-receptors in the trabecular meshwork and via the uveoscleral pathway.^{6–9} The mechanisms of this increased outflow facility may be mediated through increased intracameral levels of cyclic adenosine monophosphate (cAMP).¹⁰

The ability of the epinephrine compounds to stimulate beta- as well as alpha-receptors suggests that they may not be as effective when used with beta-adrenergic antagonists. It does appear that beta-blockers can limit the rise in cAMP and outflow caused by epinephrine on trabecular meshwork cell cultures, and this effect is less likely with the beta₂-selective antagonists.¹¹ Although controversial, beta-blockers in fact are additive to epinephrine in lowering IOP in humans.^{12–14} On the other hand, these additive effects may be small^{15,16} and even transient.¹⁷ Pretreatment and the order of administration of the two classes of drugs may play a role.¹⁸ Some investigators have shown that selective beta-blockers are more additive to epinephrine, corresponding to their reduced tendency to interfere with the effect of cAMP.¹⁹ Dipivalyl epinephrine produces a similar response.^{20,21}

The development of dipivalyl epinephrine was a breakthrough in the use of adrenergic agonists, for it allowed administration of a lower total dosage of the agonist while preserving efficacy (Figure 32–1B). The inactive pro-drug is created through a process of diesterification. This increases lipophilicity of the molecule by 100 to 600 times, which improves corneal absorption by 10-fold.²² Hydrolysis of the pro-drug to a pharmacologically active form occurs in the cornea,²³ and the two pivalic acid byproducts are nontoxic.²⁴

SIDE EFFECTS

The nonselective adrenergic agonists possess multiple ocular and systemic side effects that have historically limited their use (Table 32–1). Ocular side effects range from isolated surface disorders to functional effects that directly

TABLE 32–1 SIDE EFFECTS OF NONSELECTIVE ADRENERGIC AGONISTS

Ocular
Surface
Irritation
Inflammation (conjunctivitis)
Adrenochrome deposits
Follicular (hypertrophy) conjunctivitis
Rebound inflammation
Intraocular
Cystoid macular edema
Mydriasis
Angle-closure glaucoma
Systemic
Increased blood pressure
Extrasystoles
Bronchodilation

limit vision. Systemic side effects can be potentially dangerous in susceptible individuals.

Ocular Side Effects

Ocular surface disorders from nonselective adrenergic agonists range from mild conjunctival injection and irritation, due to rebound vasodilation following initial vasoconstriction, to a frank blepharoconjunctivitis.²⁵ Both epinephrine and dipivalyl epinephrine can produce follicular conjunctivitis (Fig. 32–2A).²⁶ However, some of the surface side effects of epinephrine may be avoided with the pro-drug, even in patients with proven intolerance to epinephrine.²⁷ Once the drug is discontinued, the conjunctivitis resolves within a month, but generally recurs with readministration.^{28,29}

Chronic administration of epinephrine can produce deposits of the melanin pigment, adrenochrome, in the conjunctiva³⁰ (Fig. 32–2B), the cornea,^{31,32} and the nasolacrimal

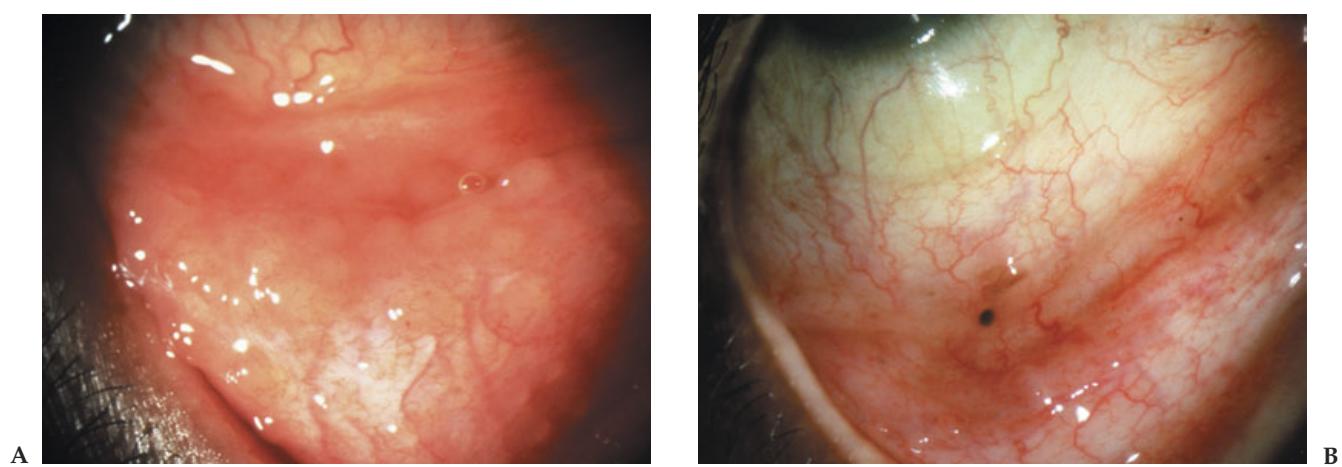


FIGURE 32–2 Side effects of nonselective alpha₂-adrenergic agonists. (A) Follicular conjunctivitis on the inferior tarsus. (B) Adrenochrome deposits. [(B) courtesy of Julia Whiteside-Michel, M.D.]

TABLE 32-2 COMPARISON OF THE SELECTIVE ALPHA₂-ADRENERGIC AGONISTS

Generic and Brand Name	Indications and Recommended Uses	Suggested Dosing	Relative alpha ₂ selectivity (alpha ₂ /alpha ₁)
Clonidine (Isoglucon)	Chronic: treatment of OHT and OAG	NR	180-fold
Apraclonidine (Iopidine)	Acute: 1% soln to reduce perioperative pressure elevations Chronic: 0.5% soln only as add-on therapy to delay surgery	Acute: immediately before and after surgery Chronic: three times daily	64-fold
Brimonidine (Alphagan)	Acute: reduce perioperative pressure elevations Chronic: reduce IOP elevations associated with OHT and OAG	Acute: immediately before and after surgery Chronic: Twice-daily, (t.i.d. in US only)	1780-fold

NR, not recommended; OHT, ocular hypertension; OAG: open-angle glaucoma.

duct, where melanin-laden casts may cause obstruction.³³ Although epinephrine can also cause staining of soft contact lenses,³⁴ a limited series of patients wearing soft contact lenses showed no such staining while using dipavaly epinephrine.³⁵

Epinephrine maculopathy, confirmed by fluorescein angiography to be cystoid macular edema, has been reported in 20 to 30% of aphakic eyes.^{36,37} This vision-affecting side effect is reversible with discontinuation of the drug but can recur when the medication is reinstated.³⁸ Aphakic cystoid macular edema is much less likely with dipavaly epinephrine, presumably due to the lower levels of active drug administered.³⁹

The mydriatic effect of epinephrine can precipitate an acute angle-closure attack. Because of this, both epinephrine and dipavaly epinephrine should be avoided in eyes with occludable angles.

Systemic Side Effects

The high concentration of topical epinephrine can produce blood levels comparable to the usual 1 mg systemic dose.⁴⁰ As many as 25% of patients using topical epinephrine can have a rise in blood pressure, an effect not observed with dipavaly epinephrine.⁴¹ Systemic adrenergic activation leading to premature ventricular contractions (extrasystoles) can

be particularly dangerous in patients with conditions such as heart disease and hyperthyroidism. As with any topically applied drug, punctal occlusion will reduce systemic uptake.

FORMULATIONS

Topical epinephrine is available as epinephrine hydrochloride, epinephrine borate, and epinephrine bitartrate in concentrations ranging from 0.5 to 2%. Dipavaly epinephrine is available in a 0.1% solution. The 0.5 and 1% doses of epinephrine are equally potent in lowering IOP, and both are more effective than the 0.25% concentration.⁴² Twice-daily dipavaly epinephrine lowers IOP as effectively as epinephrine,^{43,44} which in some studies averages 3.5 mm Hg.⁴⁵

SELECTIVE ADRENERGIC AGONISTS

The relatively alpha₂-selective adrenergic agonists represent a considerable improvement over the nonselective adrenergic agonists, being equally effective, with fewer side effects and less tachyphylaxis. These agents include clonidine, apraclonidine, and brimonidine (Table 32-2). They are all 2-imidazoline derivatives.⁴⁶ Their efficacy and side effect profile depend on their relative affinity for the alpha₂ receptor, and their lipophilicity (Figure 32-3).

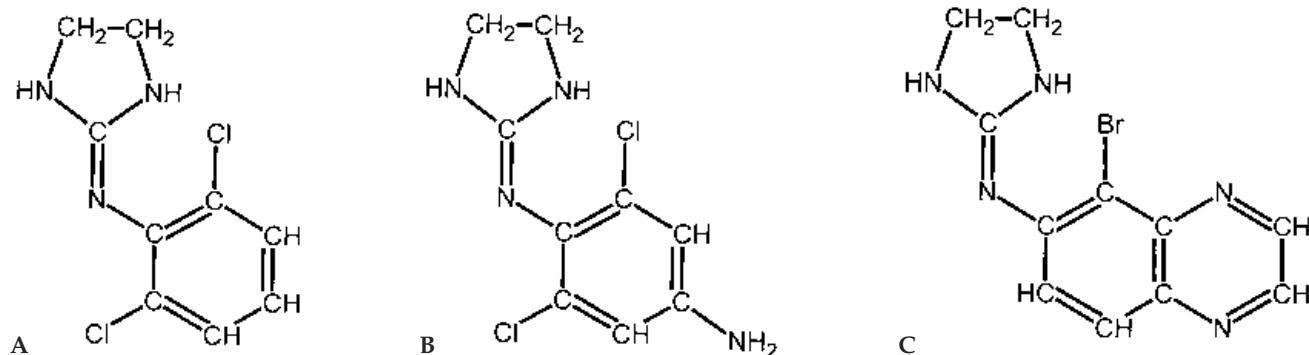


FIGURE 32-3 Selective adrenergic agonists. (A) Clonidine. (B) Apraclonidine. (C) Brimonidine.

The alpha-adrenoceptors are divided into two types, alpha₁ and alpha₂, each having at least three subtypes.⁴⁷ Although the activity of each subtype is not well understood, the two distinct alpha-adrenoceptor pathways produce a number of specific ocular effects.^{48,49} Alpha₁-mediated ocular effects include mydriasis, eyelid retraction, and ciliary vasoconstriction.^{48–50} Alpha₂-adrenergic agonists mediate reduced production of aqueous humor,^{51–54} either vasoconstriction or vasodilation, depending on the given vascular bed,⁵⁵ and possibly neuroprotection of the optic nerve.^{56–58} In the context of glaucoma, a greater alpha₂ selectivity appears to produce a more favorable therapeutic response.

CLONIDINE

Background

In the late 1970s, Harrison and Kaufmann demonstrated that topical application of clonidine effectively lowered IOP.⁵⁹ In 1983, clonidine became the first relatively alpha₂-selective agent available for the treatment of glaucoma. Although a potent inhibitor of aqueous humor production,⁶⁰ clonidine carries potentially serious adverse systemic side effects, which include systemic hypotension, bradycardia, and sedation.⁶¹ These effects are most likely due to the drug's lipophilic character because, at therapeutic topical doses, it readily crosses the blood-brain barrier.^{62,63} Because of this, clonidine is highly restricted, and it is now used for long-term treatment of glaucoma and ocular hypertension in only a few countries, mostly in Europe.

Mechanism of Action

Clonidine, the first relatively alpha-selective agent used in ophthalmology, is the most lipophilic of these agents. This property, through which it gains ready access to the central nervous system, is responsible for many of this drug's unacceptable systemic side effects, which will be discussed in the following section.

Clonidine lowers IOP primarily via reduced aqueous humor production.⁶⁰ A single drop of clonidine, both 0.125 and 0.25%, produces a significant decrease in IOP from baseline in normal volunteers, ocular hypertensives, and glaucoma patients.^{59,64} It also causes substantial IOP lowering compared with pilocarpine 2.0% in the treated eye,⁶¹ and a contralateral decrease in IOP relative to placebo.

Side Effects

Topical clonidine can produce significant, even life-threatening, systemic side effects (Table 32–3). Following intravenous administration, clonidine results in a transient increase in blood pressure, mediated by peripheral alpha₁-adrenergic stimulation (vasoconstriction). This is followed by a sustained period of systemic hypotension

TABLE 32–3 SIDE EFFECTS OF SELECTIVE ALPHA₂-ADRENERGIC AGONISTS

	Ocular	Systemic
Clonidine	Vasoconstriction, hyperemia	Hypotension, bradycardia, sedation
Apraclonidine	Ocular allergy, eyelid retraction, mydriasis, conjunctival blanching, ocular burning and stinging	Oral dryness, taste perversion, headache, fatigue/drowsiness
Brimonidine	Ocular allergy, burning, stinging, blurred vision	Oral dryness, headache, fatigue/drowsiness

due to a central nervous system (CNS) alpha₂-adrenergic sympathomimetic effect. When a therapeutic topical dose is administered, it readily gains access to the CNS and can cause clinically significant systemic hypotension, bradycardia, and sedation.⁶¹

The ability of topically applied glaucoma medications to alter blood flow in the optic nerve and posterior segment of the eye is controversial. The effects of various glaucoma medications on ocular blood flow vary with the measurement technique employed. Alpha₂-adrenergic agonists appear to mediate vasoconstriction and play a role in the autoregulation of capillary pressure and tissue oxygen delivery,^{65,66} or mediate vasodilation by stimulating the production of endothelial-derived relaxing factor.^{67,68}

PEARL... Clonidine is a potent ocular hypotensive agent and is as effective as pilocarpine 2%. Unfortunately, the systemic safety profile makes it unsuitable for routine use in glaucoma.

Although few studies examining ocular hemodynamic effects of clonidine are reported, one acute study in healthy volunteers has suggested that some glaucoma medications, including clonidine and timolol, may reduce ocular blood flow in the optic nerve head.⁶⁹ No effects on central retinal or ophthalmic artery blood flow velocities, as measured with Doppler ultrasound, were seen with any of the study medications.

APRACLONIDINE

Apraclonidine, a lipophilic analogue of clonidine, is useful for treating acute elevations of IOP. Given prior to and immediately after surgery, it can be routinely used to prevent IOP elevations following laser procedures and cataract surgery. Apraclonidine may also provide adequate IOP-lowering additivity for those patients awaiting

surgery and whose IOP remains uncontrolled on maximally tolerated medications. Many of these patients, however, fail to achieve clinical success, due either to a loss of efficacy or to drug allergy.

Background

Apraclonidine, a hydrophilic analog with reduced capacity to cross the blood–brain barrier, was designed to improve upon the systemic safety of clonidine and developed for use in ophthalmology. In 1987, apraclonidine 1% was introduced in the United States for the treatment of IOP elevations following anterior segment laser surgery. Subsequently, a 0.5% solution was approved for short-term adjunctive therapy of chronic glaucoma⁷⁰ or to delay surgery.

Mechanism of Action

This second generation, selective alpha₂-adrenergic ophthalmic agonist differs chemically from clonidine by an amino group substitution at the C₄ position of the benzene ring. This modification greatly reduces lipophilicity, and thus apraclonidine does not readily cross the cornea or blood–brain barrier.⁶³ This molecular change also increases the oxidative lability of the compound, which may encourage the development of reactive intermediates that can generate haptens, ultimately evoking an allergic response.⁷¹

Receptor affinity studies suggest that apraclonidine is less selective than clonidine for alpha₂ over alpha₁-adrenoceptors.^{72–74} Thus, at higher therapeutic concentrations, apraclonidine may produce ocular effects mediated through alpha₁ as well as alpha₂ receptors. It lowers IOP by reducing aqueous production by the ciliary body and by improving aqueous outflow through the trabecular meshwork.⁵¹

The ability to stimulate alpha₁ receptors suggests that apraclonidine may affect ocular hemodynamics. It appears to reduce conjunctival oxygen tension,⁷⁵ and it stimulates anterior segment vasoconstriction.^{76,77} Because of this, apraclonidine can help minimize bleeding during anterior segment surgical and laser procedures, in addition to preventing postoperative IOP elevations. However, in limited studies, acute treatment with apraclonidine 0.5% in normal volunteers appears to have no effect on perimacular, central retinal, or ophthalmic artery blood flow.⁷⁸ In another study, apraclonidine 1% significantly reduced ophthalmic artery blood flow in healthy volunteers but did not alter central retinal arterial blood flow.⁷⁹

Efficacy

Prophylaxis for Postoperative IOP Spikes

Apraclonidine is available as a 1% solution in a unit dose for acute usage and as a 0.5% solution for multiple dosing as short-term adjunct therapy in patients on maximally tolerated medications. Both 1 and 0.5% preparations effectively

prevent postoperative IOP spikes.^{80–83} When administered 1 hour prior to and immediately following anterior segment laser surgery, apraclonidine 1% significantly lowers postoperative IOP for over 3 hours and significantly limits the incidence of postoperative pressure elevations greater than 10 mm Hg.⁸⁰ A similar dose applied to patients receiving argon laser trabeculoplasty can reduce mean IOP from baseline more effectively than pilocarpine 4%, timolol 0.5%, dipivefrin 0.1%, or 250 mg of acetazolamide.⁸¹ Pre- and postoperative administration of 0.5% apraclonidine also appears to be adequate for most patients.⁸³ However, apraclonidine does not successfully protect all patients from postoperative pressure spikes, especially those who are already using the drug chronically.^{84,85}

PEARL... If a drug is being used chronically to control IOP, it is ineffective in blunting post-laser IOP spikes and other acute elevations of IOP in the majority of patients.

Monotherapy for Chronic Glaucoma Management

The majority of clinical trials studying apraclonidine 0.5% as long-term glaucoma therapy are of no more than 3 months' duration, and were performed with patients that were either already on, or intolerant of, other glaucoma medications. Because of this, our understanding of the clinical effectiveness of apraclonidine as chronic therapy for glaucoma is limited.

In one study, apraclonidine 0.5% t.i.d. provided peak IOP-lowering efficacy comparable to that of timolol 0.5% b.i.d.⁸⁶ However, 36% of patients receiving apraclonidine developed ocular allergy. Although another study also showed peak IOP-lowering comparable to that of timolol 0.5% b.i.d., trough IOP (before morning apraclonidine instillation) was significantly lower with timolol.⁸⁷ In long-term studies of 1 year or more, one third to one half of the patients developed allergy to the apraclonidine, leading to large numbers of patients who could not complete the study^{88,89} or who demonstrated loss of efficacy.⁹⁰

PITFALL... Although apraclonidine is effective for preventing acute postoperative pressure spikes, a high rate of allergy and loss of efficacy limit its use for chronic glaucoma management.

Apraclonidine as an Additive Agent

In one study, apraclonidine 0.5% b.i.d. added to timolol 0.5% b.i.d. produced a significant, approximately 20%, lowering of the mean IOP at peak effect.⁹¹ However, the trough IOP lowering was only 10%. Others have observed tachyphylaxis following an initial, additive response.⁹² In another study, the initially adequate additive IOP effect was lost over time.⁹³

Side Effects

Chronic use of apraclonidine, 1 and 0.5%, can produce alpha₁-mediated ocular and periocular side effects in 15 to 48% of patients, possibly due to its oxidative lability.⁸⁶⁻⁸⁸ Ocular allergy can range from mild conjunctival injection to severe blepharoconjunctivitis, with follicular reaction and induration of the eyelids (Fig. 32-4). Beyond this, the most common ocular and periocular side effects are ocular burning and stinging, eyelid retraction, mydriasis, and blanching of the conjunctival vessels (see Table 32-3).

As anticipated, chronic use does not cause clinically significant cardiovascular effects.⁶³ Infrequent, mild systemic side effects include a small, clinically insignificant slowing of the heart rate, fatigue, oral dryness, taste perversion, occasional reductions in systemic blood pressure, and headache.

BRIMONIDINE

Brimonidine is a highly selective alpha₂-adrenergic agonist.^{94,95} A 0.2% solution administered twice daily has a sustained clinical effectiveness comparable to that of timolol 0.5% b.i.d. and superior to that of betaxolol 0.25% suspension b.i.d. It also provides effective additive IOP-lowering in patients using beta-blockers, and it is not contraindicated in patients with cardiopulmonary disease. Despite a modest ocular allergy rate, the efficacy, safety, and patient acceptance of 0.2% brimonidine make it an appropriate first-line or second-line therapy or an initial additive agent for the chronic treatment of IOP in patients with ocular hypertension or glaucoma.

Background

Experience with clonidine and apraclonidine clearly demonstrated the substantial ocular hypotensive efficacy of the imidazoline-related, differentially selective alpha₂-adrenergic agonists. Brimonidine was introduced as a

drug that could produce significant lowering of IOP with fewer side effects and less tachyphylaxis than observed with either clonidine or apraclonidine.

Mechanism of Action

Brimonidine is chemically distinguished from clonidine and apraclonidine by a quinoxaline (bicyclic) ring modification and bromine substitution for chlorine. These molecular differences enhance the alpha₂ selectivity of brimonidine^{46,96} and reduce its lipophilicity relative to clonidine. Brimonidine penetrates the cornea readily,⁶³ but likely has less access to the CNS than does clonidine because it is less lipophilic and has a rapid metabolism and short plasma half-life.⁷⁴ The quinoxaline ring modification does not alter the oxidative lability of the parent molecule, giving brimonidine an oxidative stability similar to clonidine.⁹⁶

Brimonidine appears to lower IOP by reducing aqueous humor production and increasing uveoscleral outflow.⁵²⁻⁵⁴ In assays comparing the affinities for the discrete alpha₁- and alpha₂-adrenergic receptor subtypes, brimonidine displays a 1780-fold greater selectivity for alpha₂- than alpha₁-adrenoceptors (Table 32-2).⁷⁴ This represents an alpha₂-receptor selectivity that is at least 10 times greater than clonidine, and over 28 times that of apraclonidine.

PEARL... Brimonidine lowers IOP through a dual mechanism of action: it decreases aqueous production and increases uveoscleral outflow.

Bioassay experiments indicate that brimonidine has less vasoconstrictive effect on human retinal vascular tissue than either clonidine or apraclonidine.^{74,97,98} Although brimonidine, at a high enough concentration, is capable of stimulating retinal vessels, pharmacokinetic studies in rabbits and monkeys show that the vitreous humor

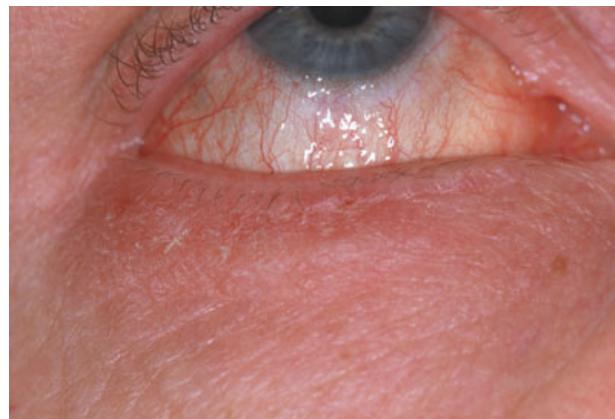


FIGURE 32-4 Side effects of selective alpha₂-adrenergic agonists. (A) Severe blepharoconjunctivitis from chronic apraclonidine use. (B) Moderate, but symptomatic, blepharoconjunctivitis from chronic brimonidine use, with erythema and scaling of the lower lid and conjunctival injection. Note the irregular light reflex on the bulbar conjunctiva, indicating the presence of follicles.

concentration following b.i.d. topical dosage for 2 weeks is much lower than the level needed to produce this effect.

In humans, short-term experiments with topical brimonidine reveal no statistically significant changes in blood flow velocity or resistance in the central retinal, ophthalmic, or posterior ciliary arteries.⁹⁹ However, one study using scanning laser Doppler flowmetry has found that a 3-day administration of topical brimonidine 0.2% t.i.d. produced a significant increase in retinal capillary blood flow.¹⁰⁰ In spite of this report, it is not clear whether brimonidine, or any glaucoma medication, has a clinically significant effect on posterior segment ocular hemodynamics.

Preclinical studies suggest that alpha₂-adrenergic agonists may also have neuroprotective properties, in addition to lowering IOP. These include neuroprotection to the inner retina following mechanical and ischemia/reperfusion injury, at concentrations may be achieved in the posterior segment with topical therapy.^{58,63,74,101} This effect is blocked by yohimbine, implicating a specific alpha₂-adrenoreceptor-dependent mechanism. Although these observations suggest that brimonidine may enhance cell survival and function in the retina and optic nerve, human clinical studies are needed to determine whether it actually provides neuroprotection in glaucoma patients.

Efficacy

Prophylaxis for Postoperative IOP Spikes

Few studies of the prophylactic utility of brimonidine for acute IOP elevations have been performed with the marketed concentration of 0.2%. However, it appears to be comparable to apraclonidine 1% in preventing IOP elevation following laser trabeculoplasty.¹⁰²

Monotherapy for Chronic Glaucoma Management

Two 1-year, multicenter, randomized, double-masked clinical trials have compared the efficacy, safety, and acceptability of twice-daily 0.2% brimonidine with that of timolol 0.5% b.i.d. in ocular hypertensive and open-angle glaucoma patients.^{103–106} A combined analysis of these studies revealed that IOP control with brimonidine was comparable to that of timolol at peak drug effect, although not quite as good at the trough (4.3 mm Hg vs 6.0 mm Hg [$P < 0.001$]).¹⁰⁶ Mean heart rate was unchanged with brimonidine, whereas timolol caused a significant slowing of the mean heart rate from baseline. Systolic and diastolic blood pressures remained stable in both treatment groups.

In a 3-month clinical trial comparing brimonidine 0.2% with betaxolol 0.25% b.i.d., the IOP-lowering efficacy of brimonidine was significantly greater at both peak and trough effect.¹⁰⁷ Neither treatment was associated with any clinically significant effects on heart rate, blood pressure, or pulmonary function.

Similar results have been obtained with two “effectiveness” studies, where clinical success is measured by

whether or not the physician would recommend continuing to treat the patient with the study medication.^{108,109} These clinical studies found comparable success rates for brimonidine (71%) and timolol (70%), and significantly higher success rates with brimonidine (74%) versus betaxolol (57%). In the latter study,¹⁰⁹ overall mean IOP decrease from baseline was 5.9 mm Hg for brimonidine and 3.8 mm Hg for betaxolol.

Brimonidine as an Additive Agent

One 3-month clinical evaluation has shown that brimonidine is safe and effective when added to beta-blockers. Brimonidine 0.2% b.i.d. lowered IOP as effectively as pilocarpine 2% when added to a beta-blocker.¹¹⁰ In the brimonidine group, the overall peak additive IOP-lowering effect was 5.0 mm Hg from baseline and 4.5 mm Hg in the pilocarpine group. Trough effects were 3.7 mm Hg and 2.9 mm Hg, respectively. Significantly higher incidences of headache and visual disturbance were reported in the pilocarpine group, whereas oral dryness was more common with brimonidine.

Side Effects

Although generally better tolerated than apraclonidine, the most common ocular side effect with brimonidine is ocular allergy, which is reported in 5 to 25% of patients.^{104,105,107,110a} This appears to vary by region and can range from mild conjunctival injection to occasionally severe follicular conjunctivitis and blepharoconjunctivitis (see Fig. 32–4B). A 0.15% concentration of brimonidine, using a different preservative, Purite, has recently been introduced to diminish the ocular side effects, and is marketed as Alphagan P. As with apraclonidine, brimonidine 0.2% does not produce clinically significant cardiopulmonary side effects.^{103–108,109,111,112} Occasional systemic side effects include fatigue, oral dryness, and drowsiness (see Table 32–3). Brimonidine is contraindicated in infants, due to the potential for severe sedation, and in patients taking monoamine oxidase inhibitors.

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ADRENERGIC ANTAGONISTS

Paul Rafuse, M.D., Ph.D., F.R.C.S.C.

The introduction of topical beta-blockers in the late 1970s transformed the medical management of glaucoma. Although topical agents prior to this time effectively lowered intraocular pressure (IOP), they carried significant ocular morbidity. Practitioners often had to moderate their desire to protect the optic nerve from chronically elevated IOP by the recognition that miotics would cause blurring of the patient's vision, and epinephrine often created an intolerably injected eye. In contrast, topically applied beta-blockers profoundly affected IOP while avoiding these side effects. Although the systemic worries of oral beta-blockers used to treat hypertension, angina, and arrhythmias were well appreciated, these side effects were initially considered unlikely to occur following eyedrops.

Over the past 20 years, topical beta-blockers have become the most widely prescribed class of glaucoma medication. Our enthusiasm for their use is tempered only by our heightened awareness that they can be systemically absorbed in amounts sufficient to cause serious pulmonary, cardiac, and perhaps metabolic effects in certain patients. These systemic adverse effects of topical beta-blockers have driven the research and development of new, topically applied classes of drugs. In clinical trials, the efficacy of these newer drugs is still compared with that of beta-blockers.

BACKGROUND

The identification of the adrenoceptors and the development of drugs to stimulate and block these membrane-bound proteins stand as milestones in the evolution of pharmacology. Alquist first clearly elucidated the pharmacological actions mediated by the two adrenoceptors, alpha and beta, in 1948.¹ Propranolol became the first pure beta-antagonist to be used clinically, and it remains

the prototype for this class of drug.² Although initially indicated for treating tachyarrhythmias, it has since been approved for hypertension, angina, migraine, and essential tremors. In 1967, Phillips and coworkers first reported that intravenous propranolol lowered IOP,³ and 1 year later, other investigators demonstrated that topically applied propranolol produced a similar result.⁴

Unfortunately, topical propranolol has membrane-stabilizing, or local anesthetic, effects on the eye, which prevented its clinical use.⁵ Another systemic beta-blocker, practolol, produced an immune-mediated oculomucocutaneous syndrome that could lead to corneal scarring and perforation.⁶ Other beta-blockers were tried and abandoned. Finally, the nonselective beta-antagonist timolol showed no serious ocular toxicity and then became available for widespread clinical appraisal in 1978.⁷

It became apparent that beta-receptors consisted of at least two, and maybe three, subtypes.⁸ Beta₁-receptors are found primarily in the heart, and their stimulation leads to an increase in heart rate and contractility. Beta₂-receptors reside in a variety of tissues including the muscles of the uterus, blood vessels, and large airways. Stimulation of beta₂-receptors in blood vessels and bronchi causes dilation of these structures; blockade of the receptors causes constriction. Beta₃-receptors may be involved in some of the metabolic effects of adrenergic agonists and antagonists such as in the modulation of lipoproteins. To avert unwanted pulmonary beta₂ blockade with nonselective agents, the relatively selective beta₁ antagonist, betaxolol, was introduced commercially in 1985.⁹ Interestingly, betaxolol produces a significant IOP-lowering effect despite the observation that 75 to 90% of the beta-receptors found in the eye (ciliary epithelium and ciliary body blood vessels) are of the beta₂ subtype.¹⁰ This raises the question of how selective and nonselective beta-blockers lower IOP.

MECHANISM OF ACTION

PHARMACOLOGY

Beta-blockers lower IOP by suppressing the formation of aqueous humor.⁷ There is little evidence that they have any significant effect on aqueous outflow. The physiology of aqueous formation is imperfectly understood but seems to involve a combination of ultrafiltration and active secretion by the ciliary epithelium (Chapter 3). Basic research on tissues rich in beta-receptors, such as heart and bronchial smooth muscle,⁸ provides a detailed explanation of the cellular events involved in beta-receptor receptor activation and blockade.

Binding of an agonist molecule to a beta-receptor stimulates a regulatory protein (G protein) to activate adenylate cyclase. This enzyme catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which acts as a “second messenger” to trigger a cascade of biochemical events. In the ciliary epithelium, cAMP is believed to regulate the ion channels and enzymes involved in the secretion of aqueous humor.¹¹ In contrast, beta-blockers cause a decrease in cAMP levels, a decrease in aqueous production, and a drop in IOP. However, the standard beta-receptor model does not entirely explain how beta-blockers affect IOP.

For adrenergic receptor blockers to have any effect at all on the eye presumes the existence of an adrenergic “tone.” Although the source of the endogenous catecholamines is unknown, they may be bloodborne as well as released from sympathetic neurons terminating in the ciliary body.¹² Beta₂-receptors exist in the ciliary blood vessels. Blockade of these receptors might result in unopposed alpha-receptor-mediated constriction and reduced blood delivery to the ciliary body and epithelium. This could lead to a reduction in the capillary perfusion pressure and a decrease in ultrafiltration and aqueous formation.¹³

Many have suggested that a simple effect on cAMP levels does not explain the receptor-mediated response to beta-blockers. Adrenergic agonists increase cAMP levels and aqueous production via a beta-receptor mechanism, but alpha-receptor stimulation should decrease aqueous inflow and enhance trabecular and uveoscleral outflow. Thus, the net effect of epinephrine will be a decrease in IOP.¹⁴ However, direct stimulators of cAMP production, such as forskolin and cholera toxin, actually lower IOP by reducing aqueous production.¹⁵ Even more difficult to reconcile is the observation that the IOP-lowering effect of timolol is the same whether the low-affinity dextroisomer or high-affinity levoisomer is used.¹⁶ A truly receptor-mediated event should show a difference in potency of several orders of magnitude between these stereoisomers.

Finally, it is unknown why a beta₁-selective antagonist, such as betaxolol, should lower IOP if the receptors responsible for mediating aqueous production are of the

beta₂ subtype. It may be as simple as recognizing that betaxolol is only relatively selective for beta₁-receptors, and the high concentrations present in the eye following a drop of 0.25 or 0.5% betaxolol will also block beta₂-receptors to some extent. This could also explain why the effect of betaxolol on IOP is generally less than the non-selective beta-blockers. It is also possible that neither betaxolol nor the nonselective agents lower IOP by blocking the beta-receptor receptor/cAMP mechanism. Polansky and colleagues have provided evidence that beta-blockers interfere with chloride conductance.¹⁷ Yu and others have reported that beta-blockers can act directly as calcium channel blockers, without involving the beta-receptor receptor at all.¹⁸

EFFICACY

In the United States, there are increasing numbers of proprietary and generic beta-blocker preparations, based on five active compounds: timolol, betaxolol, levobunolol, metipranolol, and carteolol (Fig. 33–1). The peak effect depends largely on the active, or medicinal, component of the preparation. The nonmedicinal ingredients, such as salts, buffers, surfactants, and preservatives, may influence the ocular and systemic absorption, tolerability, and duration of action. Timolol maleate, the first topical beta-blocker available, remains highly popular and provides a measuring stick for the newer beta-blockers as well as medications from other classes.

Prior to timolol, medical management of chronic glaucomas consisted of direct adrenergic agonists, direct and indirect cholinergic agonists, and oral carbonic anhydrase inhibitors. Early trials demonstrated that timolol lowered IOP better than either pilocarpine¹⁹ or epinephrine.²⁰ None of the newer beta-blockers appear to be more effective in reducing IOP than timolol. A medium-duration study showed equivalent peak effects for the alpha₂ agonist apraclonidine 0.5% t.i.d. and timolol 0.5% b.i.d.,²¹ whereas a longer comparison between timolol 0.5% and brimonidine 0.2%, another alpha₂ agonist, both dosed b.i.d., demonstrated no significant difference.²² There have been a number of clinical trials comparing the prostaglandin analog latanoprost 0.005% to timolol 0.5%. Some indicate an equal IOP-lowering efficacy,^{23,24} although another showed that the prostaglandin analog was slightly more effective.²⁵ Dorzolamide, a topical carbonic anhydrase inhibitor, and betaxolol have similar efficacies²⁶ whereas, on average, timolol lowers IOP more than dorzolamide.

Several new agents have been approved for use in glaucoma over the past several years. In general, timolols efficacy is comparable to the newer selective alpha-adrenergic agonists. On the other hand, the prostaglandin analogs usually produce greater lowering of IOP than timolol. Specific details of comparative efficacy of these compounds with timolol are discussed in Chapters 32 and 35.

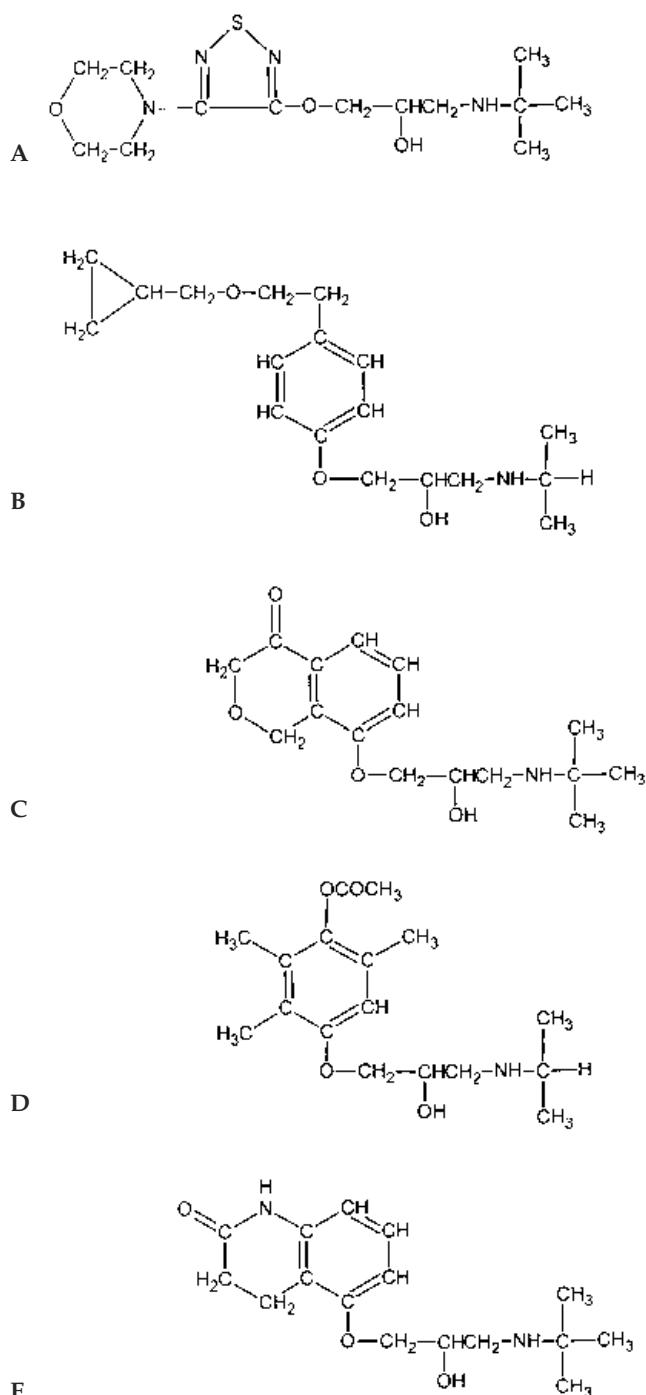


FIGURE 33-1 Beta-adrenergic antagonists used for treating glaucoma. (A) Timolol. (B) Betaxolol. (C) Levobunolol. (D) Metipranolol. (E) Carteolol.

Timolol is available in either 0.25 or 0.5% strengths. Although both concentrations produce the same peak IOP-lowering effect,²⁷ their trough effect may differ, depending on the ocular pigmentation. It seems that melanin readily binds timolol and may become a slow release depot for the drug.²⁸ Thus patients with dark irides may need a higher concentration of timolol than those

with less pigment to achieve the same response. This reasoning has led many clinicians to favor the higher drug concentration, except in patients with relative contraindications to the use of beta-blockers, such as mild asthma or borderline bradycardia. If beta-blockers are deemed necessary for children, the 0.25% concentration is preferable.

Many investigators have debated the necessity of using any of the beta-blockers more frequently than once a day.¹⁴ Most product monographs recommend and declare FDA approval for twice-daily administration. Timolol is also available in an anionic heteropolysaccharide gellan gum, which prolongs the residence time of the drug in the tear film (Chapter 31).²⁹ Clinical trials have shown that this product, given once a day, has an efficacy equivalent to twice-a-day timolol maleate.^{30,31} However, several clinical studies demonstrate that timolol maleate solutions (0.25 or 0.5%) used once every 24 hours are as efficacious as when used twice daily.^{27,32} Even though the serum half-life of absorbed topical beta-blockers may only be several hours (betaxolol is the longest at 12 to 20 hours²⁸), the ocular availability of the drug is prolonged due to the melanin binding previously noted. This depot storage phenomenon may, in part, explain the observation that at least 2 weeks is needed to entirely "wash out" the effects of timolol maleate after the drug is stopped.³³

CONTROVERSY

Patients with well-controlled IOPs and early to moderate disc damage, with or without visual field defects, may be able to reduce the frequency of their beta-blocker drops from twice to once daily. Assessments 24 hours after dosing are recommended to ensure IOP control.

In most patients, beta-blockers will reduce IOP by 20 to 40%. However, this effect will diminish in some patients following either short-term or long-term use. A partial loss of effect within the first few weeks of use, known as "short-term escape,"³⁴ usually produces IOP levels 25% less than the pretreatment IOP. It is believed that an upregulation of beta-receptor numbers accounts for this phenomenon.³⁵ Diminished effectiveness of beta-blockers over a longer period of months to years is known as "long-term drift."³⁶ A receptor, or intracellular, alteration likely underlies this effect. Clinical fluorophotometry studies have demonstrated that aqueous inflow after a year of timolol use is higher than what it was after the first week.³⁷

Many patients use systemic beta-blockers for hypertension or heart disease. Although these oral agents can also lower IOP, this effect is usually much less than from the approved topical agents, suggesting that even high serum levels deliver only limited amounts of drug to the ciliary epithelium.

SPECIAL CONSIDERATION

The initial assessment of all glaucoma patients includes a thorough medication history. Concomitant use of a systemic beta-blocker in a patient with substantial nerve damage and normal IOP suggests that the nerve damage may have resulted from higher eye pressure before the beta-blocker use. This could influence determination of the patient's target pressure.

Conversely, the systemic absorption of topically applied beta-blockers can be substantial, as evidenced by the pulmonary and cardiac side effects observed in susceptible patients. Topical ophthalmic drugs, already highly concentrated to enhance ocular penetration, are absorbed across the nasolacrimal mucosa and directly enter the venous circulation to reach the lungs, heart, and other organs, such as the fellow eye, at relatively high concentrations. Topical beta-blockers can lower IOP in the contralateral eye by up to 30% of the effect on the treated eye.³⁸ Systemic side effects of topical drugs are enhanced because they bypass the liver and avoid the "first pass" effect of the liver enzymes, which partially inactivate orally administered drugs.

SIDE EFFECTS (TABLE 33-1)

Applied topically, these agents are generally well tolerated. In particular, local ocular side effects of beta-blockers are relatively uncommon. In contrast, however, systemic side

TABLE 33-1 SIDE EFFECTS OF TOPICAL BETA-BLOCKERS

Ocular	Systemic
Blurred vision	Bronchospasm
Photophobia	Reduced heart rate and contractile force
Itching	Depression
Foreign-body sensation	Fatigue
Superficial punctate keratitis	Drowsiness
Keratitis sicca	Weakness
Corneal anesthesia	Confusion
Ptosis	Anxiety
Allergic blepharoconjunctivitis	Emotional lability Sleep disturbances Memory loss Hallucinations Decreased libido Impotence Diminished physiological response to hypoglycemia Potential altered lipid metabolism

effects, some potentially life-threatening, can occasionally lead to discontinuance of these drugs.

OCULAR SIDE EFFECTS

Compared with their predecessors, topical beta-blockers have a very favorable ocular tolerability. However, some users do note transient stinging and burning, most commonly with betaxolol hydrochloride 0.5% solution. This has led to the development of the better-tolerated 0.25% suspension, Betoptic S.³⁹ Metipranolol hydrochloride (Optipranolol) has also caused more burning and stinging than other beta-blockers,⁴⁰ and several patients in England were reported to develop a granulomatous uveitis with an early preparation of this product.⁴¹ Carteolol hydrochloride (Occupress) may be the most comfortable beta-blocker following instillation.

Other commonly reported symptoms include blurred vision, photophobia, itching, and foreign-body sensations. Objective signs consist of superficial punctate keratitis, keratitis sicca, corneal anesthesia, ptosis, and allergic blepharoconjunctivitis. As with any allergic response to topical eye medications, preservatives and ingredients other than the drug itself may be the inciting allergen. All of the beta-blocker preparations presently available in the United States use benzalkonium chloride as the preservative, except Timoptic XE (Merck) which contains benzododecinium bromide. A nonpreserved solution (Merck) is also available in unit-dose containers.

The years following the introduction of topical beta-blockers witnessed an increase in the average duration of time between diagnosis and surgery. Although this is a testament to the efficacy and generally good ocular tolerability of these drops, many surgeons also noted that the success rates for their trabeculectomies declined during this period.⁴² This prompted speculation that chronic beta-blocker application might cause changes in the conjunctiva that increase the tendency for scarring following filtering surgery. Histopathologic evidence later supported this contention by demonstrating that chronic topical glaucoma medications are associated with an increased cellularity (fibroblasts and lymphocytes) in the conjunctiva.⁴³ It is currently unknown whether the major culprits are beta-blockers, cholinergic agonists, or adrenergic agonists.

SYSTEMIC SIDE EFFECTS

Many patients cannot use topical beta-blockers because of systemic side effects. Approximately 80% of an eye-drop (volume 30 to 80 µL) passes through the proximal nasolacrimal ducts to the nasal mucosa and its microvasculature, and is equivalent to an intravenous injection. Eighty percent of one 50 µL drop of a 0.5% solution contains 200 µg of active ingredient. For an infant weighing 3 or 4 kg, or a full-sized adult with labile asthma, this amount of beta-blocker could be seriously compromising. Because drops are usually instilled in both eyes twice

TABLE 33-2 CONTRAINDICATIONS TO BETA-BLOCKERS

Moderate to severe asthma, or other reactive airway disease
Greater than first-degree heart block
Sinus bradycardia (especially in the elderly)
Left-sided heart failure
History of syncopal events
History of life-threatening depression
Brittle insulin-dependent diabetes
Dyslipoproteinemias with history of cardiovascular event

a day, and patients often squeeze more than one drop with each application, it is essential to limit systemic absorption as much as possible. Simple digital nasolacrimal occlusion, or eyelid closure, for 5 minutes can markedly reduce serum concentrations of drugs.⁴⁴

Beta-receptors exist in organs throughout the body. Nontherapeutic blockade of these receptors can produce adverse pulmonary, cardiovascular, neurological/psychiatric, and metabolic side effects. Table 33-2 outlines some of the contraindications to the use of topical and systemic beta-blockers.

Beta agonists act as bronchodilators in the treatment of asthma. Beta-blockers produce the opposite effect and there are many reported cases of status asthmaticus and death resulting from topical application of these ophthalmic agents.⁴⁵ The nonselective beta-blockers (timolol, levobunolol, metipranolol, and carteolol) are particularly contraindicated in people with a history of reactive airway diseases, such as asthma, emphysema, and chronic bronchitis. Carteolol, which has intrinsic sympathomimetic activity (ISA), or partial agonist properties, should theoretically be safer than the other agents in this group. However, the literature does not consistently support this assertion.⁴⁶ Betaxolol is relatively specific for beta₁-receptors and may be a safe alternative for very mild asthma, but several reports indicate that this drug can compromise breathing in patients with preexisting lung disease.⁴⁷ A medical specialist should be consulted if betaxolol is required by patients with any pulmonary condition.

Beta₁-receptor blockade also reduces heart rate and contractile force. This decreases cardiac output, which partially explains why these drugs lower blood pressure. Excessive reduction in blood pressure can produce cerebral hypoperfusion and syncope, whereas decreased perfusion of the heart can lead to angina, myocardial infarction, and death. Patients with compromised myocardial function can suffer congestive heart failure, heart block, or bradycardias, and exacerbation of sinus bradycardia.

In addition to decreasing cardiac output, blockade of beta₂-receptors can theoretically induce vasoconstriction by leaving alpha-receptors, which mediate vasoconstriction, free to bind circulating norepinephrine. Blood flow to organs other than the brain is reduced with propranolol.⁴⁸ This has

generated considerable discussion about the possible effects of beta-blockade on optic nerve head perfusion.⁴⁹

Blood flow in the short posterior ciliary vessels and capillaries of the proximal optic nerve is extremely difficult to measure clinically, and experimental models to study the pharmacology of beta-blockers do not satisfactorily mimic the human optic disc. Many questions remain about the effects of topically applied drugs on the posterior ocular circulation. For instance, what levels of drug can be achieved in the posterior pole? And, even if beta-blockers do achieve a vasoactive concentration at the optic disc, what are the short- and long-term effects on blood flow and tissue nutrition? Other parts of the body, more readily studied than the optic nerve, show only an initial vasospasm, with no long-lasting increase in vascular resistance.⁵⁰

Beta-blockers can also affect a patient's mood. This is not surprising given that depression likely results from down-regulation of neurotransmitter pathways in the central nervous system (CNS), and all classes of antidepressants are believed to work by increasing the availability of catecholamines and serotonin at postsynaptic receptor sites. Beta-blockers may cause a depressed state⁵¹ by blocking these receptors, or exacerbate preexisting depression.⁵² Although depression occurs more frequently with oral beta-blockers than with eyedrops, the latter gain access to the CNS by their lipophilic nature and ready transport across the blood-brain barrier.

PEARL... Depression is common and it frequently coexists with glaucoma. Although the practitioner may attribute a patient's mood to use of a beta-blocker, a drug holiday of 1 month should be considered before abandoning what may be a very effective IOP-lowering treatment. Persistent depression should prompt a psychiatric consultation, both for the patient's well-being and to determine if the beta-blocker can be restarted, along with antidepressant therapy.

Most CNS side effects have been noted with timolol. This may reflect this drug's highly lipophilic nature, or the greater clinical exposure. Table 33-1 lists other CNS effects attributed to topical beta-blockers in case reports.⁵³ Most of these patients were elderly and were often taking a variety of other medications with potential CNS side effects.

Adrenergic outflow and beta-receptors contribute to the symptomatic and physiological response to hypoglycemia. Blockade of the symptoms and signs of a low blood sugar level could seriously delay the physiological response to an insulin reaction. For this reason, oral beta-blockers are relatively contraindicated when treating cardiovascular disease in diabetics. Similarly, topical ophthalmic agents should be avoided in patients with brittle diabetes.

Systemic beta-blockers can affect lipid metabolism. Similarly, topical timolol can increase serum levels of triglycerides and decrease high-density lipoproteins (HDL) in normal volunteers.⁵⁴ Systemic beta-blockers are not recommended in patients with a history of dyslipoproteinemia-related cardiac events. Although carteolol apparently has the least effect on HDLs of the compounds presently available in the United States,⁵⁵ the clinical significance of this finding is unknown.

CURRENT FORMULATIONS

BETAXOLOL HYDROCHLORIDE

This lipophilic, selective beta₁-blocker was originally formulated for its cardioselective properties to minimize the risk of bronchospasm. Until recently, betaxolol was available both as Betoptic, which is no longer available, and Betoptic S (Alcon, Fort Worth, TX), a suspension for increased comfort.

Patients with ocular hypertension and glaucoma experienced 20 to 30% lowering of IOP with Betoptic^{56,57} and a similar effect with the 0.25% concentration, Betoptic S.³⁹ Neither betaxolol preparation appears to lower IOP as much as timolol, with most studies showing about a 2 mm Hg difference. Despite this, some published evidence shows a better preservation, and even improvement, of visual fields with betaxolol as compared with timolol,⁵⁸ which some investigators attribute to a beneficial effect on optic disc blood flow. Adding betaxolol does not augment IOP reduction in patients already receiving a topical nonselective beta-blocker.⁵⁹ However, betaxolol can produce an additive effect if combined with pilocarpine,⁶⁰ carbonic anhydrase inhibitors,⁶⁰ epinephrine,⁵⁹ or dipivefrin.⁶¹

CARTEOLOL HYDROCHLORIDE

Carteolol (Ocupress), a relatively hydrophilic, nonselective beta-blocker solution, seems to lower IOP as well as timolol in patients with open-angle glaucoma,⁶² and reduces IOP by 14 to 38% in healthy volunteers with normal IOP.⁶³ Few reports elaborate on its additivity to other classes of glaucoma medications, but it appears generally comparable to the other nonselective beta-blockers in this regard. Currently, no studies address its long-term effect on visual fields in patients with glaucoma.

LEVOBUNOLOL HYDROCHLORIDE

Used twice daily, levobunolol (Betagan), a lipophilic, nonselective beta-blocker solution, and timolol provide equally effective long-term IOP control.⁶⁴ In selected patients, once-daily administration of levobunolol 0.25% may adequately control IOP for 24 hours.⁶⁵ The prolonged action of this agent probably results from its binding and slow release from ocular melanin, combined with its metabolism to dihydrobunolol, which also has beta-

blocking activity. Levobunolol is as additive to pilocarpine as timolol⁶⁶ and is minimally additive to dipivefrin, similar to other nonselective beta-blockers.⁶⁷

METIPRANOLOL

Experience in Britain and mainland Europe with this nonselective, lipophilic beta-blocker solution demonstrated a similar IOP-lowering efficacy to timolol⁴⁰ and levobunolol.⁶⁸ The prolonged duration of action of metipranolol is optipranolol attributed to a beta-blocking metabolite, des-acetyl metipranolol. Most consider its additivity to the other classes of glaucoma medications as similar to timolol and levobunolol.

TIMOLOL MALEATE

This lipophilic, nonselective beta-blocker solution is available in three preparations from the original manufacturer, as well as several recently introduced generic preparations. Aside from Timolol solution, Timolol is available in occudose, a preservative-free formulation. Timolol also is formulated with gellan gum (Gelrite), a surface-activated gel, to prolong ocular contact and improve penetration. This preparation (Timoptic XE) used once daily has the same IOP-lowering efficacy as twice-daily Timoptic solution.^{30,31} Patients will notice blurring that usually lasts for several minutes after instillation.

TIMOLOL HEMIHYDRATE

The safety and efficacy of timolol hemihydrate 0.5%, a lipophilic, nonselective beta-blocker solution, is comparable to timolol maleate 0.5%.⁶⁹

GENERIC PREPARATION

An increasing number of generic beta-blocker preparations have appeared on the market. Provided that the active ingredients are the same, these products should produce similar peak effects on IOP. However, the duration of action and tolerability (ocular and systemic) of these new products may differ depending on their non-medicinal constituents.

COMBINATION PREPARATIONS CONTAINING BETA-BLOCKERS

A combination preparation of timolol maleate 0.5% and dorzolamide 2% (Cosopt) is now available. One large study shows that Cosopt b.i.d. is comparable to the concomitant use of dorzolamide 2% t.i.d. and timolol 0.5% b.i.d.⁷⁰ Expected local and systemic side effects should be a composite of both classes of drug.

TimPilo (timolol maleate 0.5% and pilocarpine 2 or 4%) is now available as a twice-daily combination therapy

in Canada and several European countries, its active ingredients mixed with an alkaline buffer to prolong the action of the pilocarpine. As with other combination strategies, the individual drugs will influence the tolerability of this product.

A fixed combination of 0.005% latanoprost and 0.5% Timolol maleate has been compared to each of the drugs separately in glaucoma and ocular hypertensive patients. The fixed combination, administered once daily, was well tolerated and as effective in lowering IOP as either of the component drugs used separately.⁷¹

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CHOLINERGIC AGENTS

Robert J. Derick, M.D.

Cholinergic agents all lower intraocular pressure (IOP) by improving aqueous outflow. These medications differ, however, by the manner in which they stimulate ciliary muscle contraction. The most commonly used cholinergic agent is pilocarpine, which directly stimulates the cholinergic receptor. Cholinesterase inhibitors, such as echothiophate and physostigmine, work indirectly by inhibiting the enzyme acetylcholinesterase and thus prolonging the duration of action of endogenous acetylcholine. Carbachol has both a direct and an indirect effect. The most notable side effects of miotics (myopia, brow ache, and miosis) limit the widespread use of these agents for treating chronic glaucoma. However, they remain effective pressure-lowering agents and still can play an important role in managing specific glaucoma situations.

BACKGROUND

The cholinergic agents are our oldest glaucoma medications. In 1876, Laquer introduced the cholinesterase inhibitor, physostigmine, which was isolated from the calobar bean, the seed of the plant *Physostigma venenosum*.¹ One year later, Weber first treated glaucoma with pilocarpine, a derivative from the leaf of the South American shrub *Pilocarpus microphyllus*.² These two medications were the only successful glaucoma agents available until the turn of the 20th century.^{3–5} Although we now have many effective glaucoma medications, cholinergic agonists have a proven track record and are still helpful in selected glaucoma patients.

MECHANISM OF ACTION

PHARMACOLOGY

The term *cholinergic agents* refers to medications that mimic the effect of acetylcholine. Acetylcholine is a neurotransmitter at postganglionic parasympathetic junctions, some

postganglionic sympathetic endings, autonomic ganglia, somatic nerve endings, and in the central nervous system. It is synthesized by the enzyme choline acetyltransferase and activates the cell by binding to cholinergic receptors.

Acetylcholinesterase, strategically present in the end-plate region, rapidly hydrolyzes acetylcholine to limit its duration of action. The cholinergic drugs act either directly, by mimicking acetylcholine at the neuromuscular junctions (direct-acting cholinergic agonists), or indirectly, by inhibiting cholinesterase, thereby retarding acetylcholine degradation and potentiating its effect (cholinesterase inhibitors).

Cholinergic receptors are either muscarinic or nicotinic. Muscarinic receptors reside in the smooth muscle (e.g., ciliary body) and glands, and are stimulated by muscarine and inhibited by atropine. Nicotinic receptors exist in skeletal muscle and autonomic ganglia, and are antagonized by decamethonium and hexamethonium, respectively.

The effect of a cholinergic medication depends, in part, on its selectivity to preferentially interact with one receptor over another. The effect of a medication also depends on the location of its receptor. In the eye, the parasympathetic nervous system innervates the ciliary body and iris sphincter. Thus, while a cholinergic agent contracts the longitudinal muscle of the ciliary body and increases aqueous outflow, it will also stimulate the circular muscle of the ciliary body and the iris sphincter, producing accommodation and pupillary constriction.

Outside the eye, the parasympathetic nervous system controls many important functions of the body. In contrast to the adrenergic nervous system, which regulates the fight or flight response of the body and prepares the body for strenuous muscular activity; the parasympathetic nervous system modulates certain actions of the cardiovascular and digestive system and is principally involved in accumulation, storage, and preservation of body resources (Table 34–1).

TABLE 34-1 SYSTEMIC AND OCULAR RESPONSE TO ADRENERGIC AND CHOLINERGIC NERVE STIMULATION

Organ	Adrenoceptor Type	Adrenergic System Adrenergic Response	Cholinergic System Cholinergic Response
Heart			
rate	beta ₁	Increase	Decrease
contractile force	beta ₁	Increase	None
Bronchial muscle	beta ₂	Relax	Contract
GI tract (tone motility, secretions)	alpha, beta ₁	Decrease	Increase
Sphincters	alpha	Contract	Relax
Urinary bladder			
detrusor	beta	Relax	Contract
trigone sphincter	alpha	Contract	Relax
Glycogenolysis	beta	Increase	None
Lipolysis	beta ₁	Increase	None
Insulin secretion	alpha	Decrease	Increase
Eye			
pupil size	alpha	Dilate	Constrict
accommodation		None	Contract
conjunctival vessels	alpha ₁	Constrict	Dilate

MECHANISM OF INTRAOCULAR PRESSURE REDUCTION

Cholinergic medications lower IOP by increasing aqueous humor outflow, a result of muscarinic receptor-mediated contraction of the ciliary muscle. Ciliary muscle activation can have two opposing effects on aqueous outflow. First, because the anterior portion of the ciliary muscle inserts into the scleral spur, trabecular meshwork, and Schlemm's canal, contraction widens the spaces within the trabecular meshwork and Schlemm's canal. This decreases resistance and facilitates aqueous outflow via

the conventional route (Fig. 34-1A,B). However, aqueous humor also leaves the eye via uveoscleral outflow, following a pressure gradient between the ciliary muscle bundles and into the suprachoroidal space. Contraction of the muscle diminishes the space between muscle bundles and obstructs this pathway.⁶ Although initial work showed that the uveoscleral route accounts for only 10 to 20% of normal outflow in humans,⁷ more recent studies demonstrate that it accounts for as much as 50% of total outflow, particularly in younger individuals (Chapter 4). In spite of this, miotics still produce a net reduction in IOP,⁸ suggesting that the positive effect of ciliary muscle

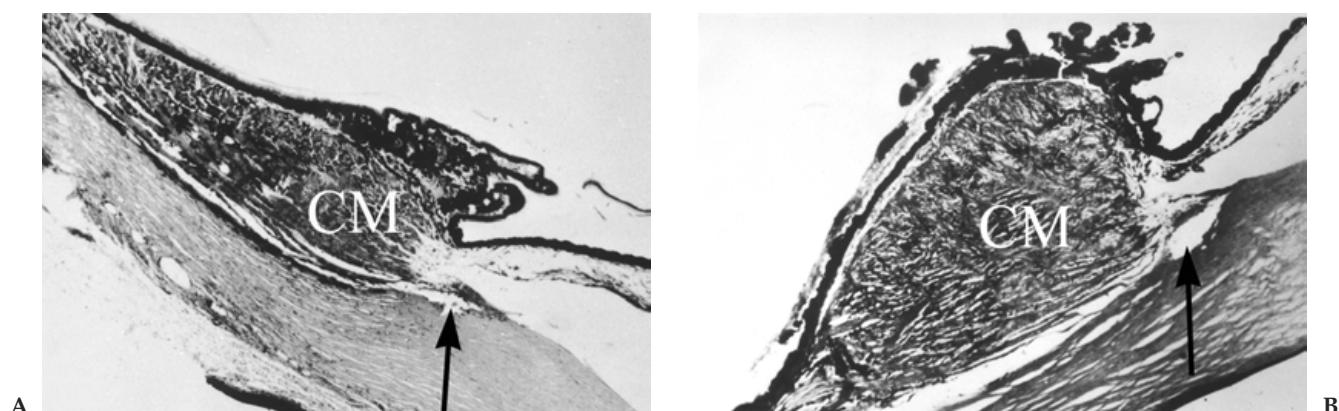


FIGURE 34-1 Differential effect of (A) atropine and (B) pilocarpine on the monkey Schlemm's canal and ciliary body. Note marked contraction of ciliary muscle (CM) and opening of Schlemm's canal (arrow) following instillation of pilocarpine. (From Kaufman, PA. Morphological changes in primate aqueous humor formation and drainage tissues after long-term treatment with antiglaucomatous drugs. *J Glaucoma* 1993;2:316–328. With permission.) (Courtesy of Paul Kaufman, M.D.)

contraction on conventional outflow is significantly greater than the negative effect on uveoscleral outflow.

These mechanisms have been well documented. Severing the anterior tendon of the ciliary muscle from the scleral spur in cynomolgus monkeys abolishes the effect of pilocarpine on outflow.⁹ Cholinergic drugs do not directly affect the trabecular meshwork, nor do they significantly alter aqueous production.¹⁰ Pilocarpine primarily reaches the ciliary body through the cornea,¹¹ where the drug is largely metabolized, allowing only a small percentage to enter the eye.¹²

SIDE EFFECTS

OCULAR

Ocular side effects related to contraction of the iris and ciliary body are common with cholinergic agents and frequently lead to discontinuation of the medication (Table 34-2). Miosis can degrade vision, particularly in elderly patients with cataracts. In patients with a posterior subcapsular cataract, the miosis exaggerates the effect of a central media opacity, whereas patients with nuclear cataracts may become more symptomatic in conditions of low illumination.

Ciliary muscle contraction, particularly in young patients, can produce a severe headache and accommodative myopia. The headaches, a result of the muscle spasm, are worse at the onset of therapy and can be less troublesome if the physician warns the patient of this potential and begins therapy at a low concentration and frequency (e.g., pilocarpine 0.5% at bedtime). The induced

myopia, which can exceed 5 diopters, results from axial thickening and forward displacement of the lens. This effect begins 15 minutes after instillation of 2% pilocarpine, peaks at 45 minutes, and lasts for 1 to 2 hours, making it difficult to provide stable vision for a young patient using a single spectacle correction.¹³ To date, efforts have failed to dissociate the accommodative and miotic response of cholinergic agents from their beneficial effect on outflow facility.

PEARL... To improve acceptance and compliance, the physician should warn the patient of expected side effects prior to starting cholinergic medications. Acetaminophen, 30 minutes before instilling pilocarpine, may help palliate the ciliary spasm discomfort.

Cholinergic agents can also increase the permeability of the blood–aqueous barrier¹⁴ and aggravate ocular inflammation. This effect is dose related and is more likely with the indirect-acting agents.¹⁵ Chronic inflammation from long-term miotic use encourages posterior synechiae and can produce an adherent and miotic pupil, both of which can complicate cataract surgery. Because these agents can also increase postoperative inflammation, patients should discontinue an indirect-acting agent, or at least switch to a weaker miotic, 2 weeks prior to intraocular surgery. Cholinergic agents are also relatively contraindicated in the treatment of glaucoma associated with uveitis.

Miotics have also been implicated in causing rhegmatogenous retinal detachments, possibly by vitreoretinal traction due to ciliary body contraction. Although the evidence for this is indirect,^{16–18} the peripheral retina should be examined prior to beginning miotics, and higher-strength, direct-acting agents should be used cautiously in patients with high myopia and lattice degeneration, while avoiding indirect agents altogether.

Miotic cysts most commonly result from indirect-acting cholinergic medications, although they can also follow long-term use of pilocarpine (Fig. 34-2A,B). These cysts result from the proliferation of iris pigment epithelium near the pupillary margin and generally decrease in size after discontinuation of therapy.¹⁹ Phenylephrine may decrease the incidence and size of these cysts.

In general, the frequency and severity of ocular and systemic side effects from indirect-acting cholinergics exceed that of the direct agents. For example, although pilocarpine has been suggested to produce cataracts,²⁰ the evidence for this effect is more conclusive with the anticholinesterases.^{21–23} Typically, anticholinesterase cataracts begin with anterior subcapsular vacuoles.²² The prevalence of cataract formation increases with longer treatment duration, higher drug concentration, greater application frequency, and in older patients, particularly those with preexisting cataractous changes.

TABLE 34-2 SIDE EFFECTS OF TOPICAL CHOLINERGIC MEDICATIONS

Ocular

Miosis
Accommodative spasm, headache
Induced myopia
Increased permeability of the blood–aqueous barrier
Retinal detachment
Pupillary border cysts*
Anterior subcapsular cataracts*

Systemic

Depression of serum cholinesterase activity**
Nausea
Diarrhea
Sweating
Salivation
Bronchoconstriction
Decreased blood pressure

*More likely with indirect-acting agents.

**Specific to indirect-acting agents.

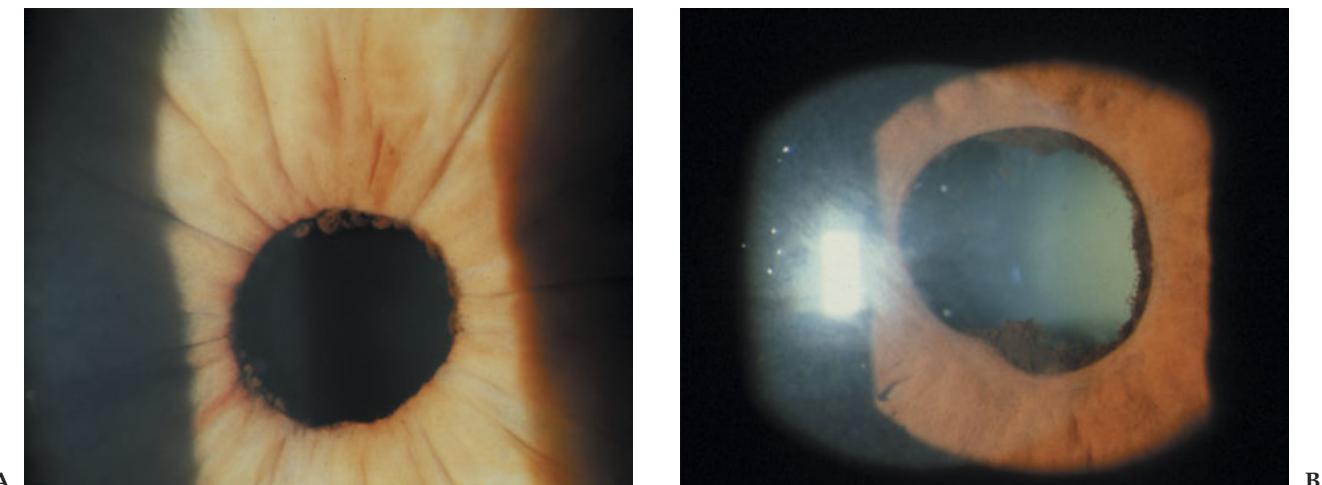


FIGURE 34-2 Complications of long-term use of cholinergic agents include (A) pupillary margin cysts and (B) posterior synechiae, combined in this case with cysts. (Courtesy of E. Michael Van Buskirk, M.D.)

SYSTEMIC SIDE EFFECTS

Frequently instilled direct-acting cholinergics, and the stronger, indirect-acting compounds, can produce systemic side effects of parasympathetic overstimulation (Table 34-2). Most of these correspond to the known distribution and actions of cholinergic receptors (Table 34-1). Nausea, diarrhea, sweating, salivation, bronchoconstriction, and a fall in blood pressure have all been reported with physostigmine.

The indirect-acting agents can also depress serum cholinesterase, or pseudocholinesterase, in addition to acetylcholinesterase, which can occur in almost all patients using as little as 0.06% echothiopate. This presents an important, adverse drug interaction when succinyl choline, which is hydrolyzed by pseudocholinesterase, is used during induction of general anesthesia. Because this inhibition can also prolong the action of succinylcholine and can produce sustained apnea, patients using these drugs should be warned of this potentially life-threatening side effect and switched to a direct-acting cholinergic drug at least 2 weeks prior to any anticipated surgery and general anesthesia.

PITFALL... Patients using cholinesterase inhibitors are at risk for prolonged apnea following use of succinylcholine and should switch to an indirect agent prior to undergoing any elective surgery.

CURRENT FORMULATIONS

All cholinergic medications have the same basic effect on aqueous humor dynamics. They differ primarily in their duration of action and the severity of their side effects.

DIRECT-ACTING AGENTS

Pilocarpine

Pilocarpine is our most commonly used miotic. Today, it is rarely used as first-line therapy because other medications have either fewer ocular side effects or a more convenient dosing schedule. Its efficacy, cost, and lack of systemic effects, however, make pilocarpine attractive as a second-line agent in many patients.

Chronic use studies demonstrate that the response correlates with dosages ranging from 0.5 to 4% concentration, with an IOP reduction of approximately 20%.²⁴⁻²⁶ Higher concentrations may provide added effect in patients with dark irides.²⁷ The maximum IOP reduction occurs within 2 hours of instillation and lasts for at least 8 hours with a 10 to 15% reduction in IOP still present at 12 to 15 hours.²⁶ Although most patients use pilocarpine three or four times daily, twice-daily instillation of 2% pilocarpine can lower IOP to a similar degree if combined with forced eyelid closure or nasolacrimal occlusion.²⁸ Because this may not apply to everyone, however, pressures should still be checked 8 to 12 hours after drug instillation in any patient using pilocarpine less than every 6 hours to insure adequate IOP control.

Younger patients, as well as some older patients with cataracts, tolerate pilocarpine poorly because of ciliary muscle spasm and induced myopia. Various pilocarpine delivery systems have been developed to decrease these side effects, as well as reduce the frequency of administration.

Pilocarpine Gel (Pilopine)

Pilocarpine gel, the equivalent of 4% pilocarpine hydrochloride in a high-viscosity acrylic gel, reduces IOP for up to 24 hours when applied at bedtime.²⁹ Although

this produces fewer ocular side effects,³⁰ the IOP can rise significantly after 12 hours. In addition, 25% of patients develop a superficial corneal haze that can decrease vision and may persist even after the gel is discontinued.³¹

Membrane-Controlled Delivery System (Ocusert)

The Ocusert Pilo-20 and Pilo-40 are diffusion-controlled inserts using ethylene vinyl acetate polymeric membranes that release pilocarpine at either 20 µg/hr (Ocusert 20) or 40 µg/hr (Ocusert 40) for approximately 1 week, producing pressure-lowering effects equivalent to 1 to 2%, and 4% pilocarpine, respectively.^{32–35} The insert is placed in the superior cul-de-sac and can be effective for 7 days, although individual patients may respond for less than 1 week.^{30,36} Because the controlled delivery minimizes the total amount of drug needed to lower IOP, this preparation limits ocular side effects. However, some patients find the membrane uncomfortable and difficult to keep in place. In addition, the Ocusert can periodically release increased amounts of drug and produce intense symptoms, especially when it is first inserted. The Ocusert is no longer commercially available.

Aceclidine

Aceclidine is a synthetic cholinergic drug that acts directly on muscarinic receptors in a manner similar to pilocarpine. The IOP lowering of 4% aceclidine is comparable to 2% pilocarpine, but produces less accommodative spasm.^{15,37} This drug is currently unavailable in the United States.

Carbachol

Carbachol is a synthetic combination of portions of the molecules of acetylcholine and physostigmine and is considered a combination direct- and indirect-acting cholinergic agent. Although it principally stimulates muscarinic receptors, it also inhibits acetylcholinesterase. Because carbachol is not lipid soluble at any pH, it penetrates the intact corneal epithelium poorly and must be formulated with an adjuvant, such as benzalkonium chloride, to help it reach effective intraocular concentrations.³⁸

Carbachol is available in 0.75, 1.5, and 3% strengths and is usually administered three times a day. Although the 1.5% concentration three times daily lowers IOP similar to 2% pilocarpine four times daily,³⁹ carbachol produces more brow ache and accommodative spasm, probably due to its indirect cholinergic properties.⁴⁰ These same properties make carbachol an effective intraoperative agent for producing miosis and guarding against postoperative IOP elevation; its intracameral formulation (Miostat) provides better protection against postcataract surgery IOP rise than either acetylcholine (Miochol) or topical levobunolol.^{41,42}

INDIRECT-ACTING AGENTS

Echothiophate Iodide

Echothiophate iodide (Phospholine iodide) is a potent inhibitor of both true cholinesterase and pseudocholinesterase. This agent, available in concentrations of 0.03 to 0.25% and administered every 12 to 48 hours, has a peak IOP effect of 4 to 6 hours and can act for at least 24 hours.⁴³ Due to limited stability, the solution should be refrigerated. Echothiophate, however, has a much longer duration of action than pilocarpine; the 0.06% solution lowers IOP comparable to 2% pilocarpine.⁴⁴ Although 0.06% echothiophate is at the top of the dose response curve for most patients, 0.125% may further lower IOP in patients with dark irides.

Unfortunately, the significant side effects of this drug offset its advantages of efficacy and duration of action. Because echothiophate, like other indirect-acting cholinergic agents, can induce dose-related, anterior subcapsular cataracts,⁴⁵ it is used primarily in aphakic and pseudophakic individuals. In addition, the indirect-acting agents are more likely than pilocarpine to disrupt the blood–aqueous barrier, which can cause increased inflammation after intraocular surgery, as well as aggravate uveitis. Therefore, most practitioners will switch a patient from echothiophate to pilocarpine several weeks prior to intraocular surgery and avoid its use in patients with uveitis.

Systemic toxicity is more common with the anti-cholinesterases. Echothiophate iodide depletes both true cholinesterase (acetylcholinesterase) and serum cholinesterase (pseudocholinesterase). Pseudocholinesterase hydrolyzes succinylcholine, and prolonged respiratory paralysis can occur after general anesthesia if succinylcholine is used on a patient with a depleted supply of pseudocholinesterase. Parasympathomimetic toxicity can also occur with these agents, producing diarrhea, nausea, and bronchospasm.

Physostigmine

Physostigmine (Eserine) is a short-acting inhibitor of cholinesterase. It is administered as a 0.5% ointment twice daily and has a longer duration of action than pilocarpine. The pressure reduction begins within 10 to 30 minutes of instillation, with maximal effect in 1 to 2 hours.⁴⁶ Aqueous solutions of physostigmine are unstable. Ocular allergy and irritation limit its long-term use.

Demecarium

Demecarium bromide (Humorsol) is a long-acting cholinesterase inhibitor similar to echothiophate in efficacy and side effects. It is administered in a solution of 0.12 to 0.25% every 12 to 48 hours. After a single dose of

demecarium, reduction of IOP occurs in half an hour, is maximal at 24 hours, and can persist for several days.⁴⁷ It is water soluble and stable at room temperature but is no longer available in the United States.

CURRENT USE OF CHOLINERGIC AGENTS

Newer, better-tolerated agents have supplanted miotics for the treatment of chronic glaucoma. However, these remain effective pressure-lowering agents and they are still useful in specific clinical situations.

ADJUNCTIVE THERAPY

Many glaucoma patients require more than one glaucoma medication to control their IOP. In these patients, the cholinergic agents can be effective as adjunctive therapy. The cholinergic agents are particularly useful as adjuncts in pseudophakic or aphakic patients because these patients tend to have fewer ocular side effects from either miosis or induced myopia.

PEARL... Cholinergic agents are usually better tolerated by pseudophakic or aphakic patients, who are less likely to be affected by miosis and ciliary muscle spasm.

The effect of the cholinergic agents on IOP is generally additive to the other glaucoma medications. Of the possible adjunctive uses for the cholinergic drugs, the beta-blockers provide one rational combination. Because the beta-blockers lower IOP by decreasing aqueous production, it is not surprising that the action of the cholinergic agents to increase outflow would be synergistic. The addition of pilocarpine 2% to timolol results in an additional 10% decrease in IOP in patients with ocular hypertension, whereas the addition of pilocarpine 4% decreases IOP an additional 15 to 20% in a similar group of patients.⁴⁸ The cholinergic medications can also be useful in combination with the carbonic anhydrase inhibitors, the alpha₂ agonists, and epinephrine.⁴⁹⁻⁵¹

Because prostaglandins lower IOP by increasing uveoscleral outflow, and the cholinergic medications decrease uveoscleral outflow, one would expect that these drugs would counteract each other when used in combination. Although the additivity of physostigmine to latanoprost is less than predicted by the full effect of the individual drugs, using the two agents together can produce some additional IOP lowering in certain cases (Chapter 35).⁵²

ACUTE ANGLE-CLOSURE GLAUCOMA

Topical pilocarpine can effectively treat acute angle-closure glaucoma (Chapter 16). Several drops of 1 to 2% pilocarpine can cause miosis, help break pupillary block, and facilitate laser iridotomy. However, in some patients, elevated IOP can render the iris sphincter ischemic and unable to respond to the pilocarpine. After the first 30 minutes of the attack, using pilocarpine more than every 2 to 3 hours provides no additional benefits and can result in systemic toxicity. Stronger miotics are contraindicated because they can displace the lens-iris diaphragm forward and aggravate the angle closure. Although prophylactic miotics have been advocated in the contralateral eye, acute angle closure can still occur despite this treatment.⁵³ Therefore, prompt iridotomy constitutes the preferred treatment for both the affected eye and the contralateral eye.

LASER IRIDOTOMY

Pilocarpine 1 to 2 % can be administered 20 minutes prior to laser iridotomy with the 2% concentration reserved for dark irides. The miotic pupil and thinner iris facilitates the laser procedure. Patients should be warned of the probable ciliary spasm and can be pretreated for this with acetaminophen to minimize discomfort.

PLATEAU IRIS SYNDROME

In certain phakic patients, the iris and cornea remain apposed despite a patent iridotomy. In these patients with plateau configuration, pilocarpine can open the angle, prevent the formation of peripheral anterior synechiae, and lower IOP.

PIGMENTARY GLAUCOMA

The miosis induced by pilocarpine can increase relative pupillary block, thus changing the iris contour from concave to flat or convex. This minimizes contact of the iris with lens zonules and thus can prevent iris pigment release (Chapter 19). Unfortunately, most patients with pigment dispersion are young and tolerate the accommodative spasm poorly. An alternative is the Ocusert, which gradually releases the medication and can improve tolerance. A more serious concern is the risk of retinal detachment from the use of miotics because patients with pigment dispersion are usually myopic and already at increased risk for this complication.⁵⁴ A careful peripheral retinal exam is recommended prior to initiating therapy.

INITIATING THERAPY

To improve patient acceptance, therapy with cholinergic agonists medications should be started at a low concentration and frequency, such as pilocarpine 0.5% at bedtime.

The physician should instruct the patient on eyelid closure following instillation, which can increase the duration of action of the medication and allow twice daily dosing in many patients. The patient should also be warned of expected side effects prior to initiating therapy. For the first week, acetominophen taken 30 minutes before each pilocarpine dose can diminish the headache and improve acceptance and compliance. The IOP should also be checked immediately prior to a scheduled dose to help assure adequate IOP control throughout the dosing interval. Patients receiving long-term cholinergic agents should undergo repeat gonioscopy to detect insidious, progressive angle narrowing due to forward movement of the lens–iris diaphragm and pupillary block.

PITFALL... After initiating therapy with a cholinergic medication, gonioscopy should be repeated to detect cholinergic-induced angle narrowing.

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PROSTAGLANDIN ANALOGS

David Lawlor, M.D., Carol B. Toris, Ph.D., and Carl B. Camras, M.D.

Prostaglandins (PGs) are a class of ubiquitous local hormones, known as autacoids, with various, sometimes conflicting, effects that are mediated through multiple types of receptors. Although their ocular effects have been known for some time, investigators have only recently succeeded in separating their ability to lower intraocular pressure (IOP) from their other, less desirable, side effects. The resulting PG formulations constitute our most potent glaucoma drugs; they lower IOP as well or better than other glaucoma medications, but at concentrations that are orders of magnitude lower. Because these unique agents reduce IOP predominantly by increasing uveoscleral outflow, PG analogs are often additive to most other glaucoma medications.

Acting as local hormones, PGs are quickly inactivated systemically. Because of this, and their low therapeutic concentrations, these agents have relatively few systemic side effects. However, as relative newcomers to the glaucoma armamentarium, their long-term side effects are largely unknown. Time and experience will continue to reveal the absolute safety and complete side effects of the PG analogs.

BACKGROUND

In 1955, Ambache, working with isolated rabbit iris exposed to hydrocarbon solvents, described an active substance that he termed irin, which had prolonged biological effects on smooth muscle.¹ These effects included the ability to constrict dilated pupils in cats when injected intraocularly. We now know that irin consisted of a mixture of the E and F type PGs, as well as other active eicosanoids.² Samuelsson determined the structure of PGs and classified them into a chemically distinct family of compounds.^{3,4}

Further study in several animal species showed that PGs could produce marked ocular irritation and inflammation. In rabbit eyes, injection of PGs caused blood–aqueous

barrier breakdown, iris vascular congestion, and elevated IOP.^{5,6} However, because of their accentuated ocular inflammatory reaction, rabbits may be poor models for human studies.⁷ By contrast, humans with clinical anterior uveitis, which often is associated with ocular hypotony, were found to have increased levels of PG in their aqueous humor.⁸ This suggested that PGs could reduce IOP.⁹ Further studies in animals supported this notion⁹ but revealed a marked species variability to PG application. For example, whereas high doses of PGs reduced IOP in monkeys,¹⁰ similar doses in rabbits initially raised IOP.⁹

The effects of a PG on the human eye were first reported in 1985.¹¹ Using the tromethamine salt of PGF₂, this and additional studies showed that although this compound reduced IOP for at least 24 hours, it also caused pronounced conjunctival hyperemia and ocular discomfort for 2 to 3 hours following instillation.^{11,12}

The less polar isopropyl ester (IE) was the next analog of PGF₂ studied in humans. Theorizing that its increased lipid solubility should improve corneal penetration, investigators anticipated that much lower doses of this pro-drug could be equally effective at lowering IOP, but with fewer side effects. Subsequent tests of PGF₂-IE in normotensive,¹³ ocular hypertensive, and glaucomatous^{14,15} eyes yielded IOP reductions of 4 to 6 mm Hg lasting at least 8 days. Although side effects were reduced in comparison to the tromethamine salt, many patients still reported significant discomfort and hyperemia.

The search continued for a more tolerable, yet still efficacious, PG analog. Ocular application of a carbon 17-phenyl substituted PGF₂ analog (PhXA34) in normotensive volunteers proved more tolerable yet still effective in lowering IOP.¹⁶ This preparation produced a sustained (1 week) 20 to 30% reduction in IOP in both ocular hypertensive and glaucomatous subjects¹⁷ with minimal discomfort and hyperemia. Whereas PhXA34 is an epimeric mixture with components of variable potency,

later clinical trials concentrated on the action of the more potent 15 R-epimer, PhXA41, dubbed latanoprost. Multi-center trials in the United States,¹⁸ United Kingdom,¹⁹ and Scandinavia²⁰ led to approval by the U.S. Food and Drug Administration in 1996 and marketing of latanoprost for glaucoma therapy. Subsequently, unoprostone, travoprost, and bimatoprost have all become available for clinical use.

MECHANISM OF ACTION

SITE OF ACTION

The exact site of action for the IOP-lowering effect of PGs is likely in the ciliary muscle. FP receptors are widely distributed in the eye and have been detected in the cornea, conjunctiva, iris, and ciliary processes, as well as the ciliary muscle.²¹ On a cellular level, connective tissue fibroblasts also contain FP receptors, whereas cell cultures show that ciliary muscle and retinal pigment epithelium can also express this receptor.²¹ The wide distribution of FP receptors in the eye suggests that PGs can produce a multitude of effects. Similarly, the reduced side effects of latanoprost compared with PGF_{2α} suggests that different cell types in the eye can have unique and specific responses to different PGs. Studies so far have not revealed any evidence for different FP receptor subtypes.

PG analogs appear to offer a unique mechanism for reducing IOP. Both direct measurements²² and indirect calculations^{23–25} indicate that these agents primarily reduce IOP by increasing uveoscleral outflow. The precise mechanism by which PGs increase uveoscleral outflow is unclear, but it is possibly related to structural modification of the extracellular matrix in the ciliary muscle.^{26,27}

Mapping studies using radioactive albumin demonstrate that the uveoscleral outflow pathway enables passage of aqueous humor from the anterior chamber through the iris root and uveal meshwork into the interstitium of the ciliary muscle and the suprachoroidal space (Chapter 4). Flow continues through perivascular channels and collagen of the sclera into the low-pressure orbital tissues, or alternatively enters the uveal vasculature. The contribution of this uveoscleral pathway to total aqueous outflow has been measured at 35 to 60% in normal monkeys,²⁸ and less than 15% in diseased elderly human eyes,²⁹ but higher in younger and even older healthy subjects.³⁰

A number of methods have been used to investigate the mechanisms of PG action.^{13,15,16,24,25,31–34} The accumulated evidence of studies in normotensive volunteers and ocular hypertensive patients suggests that PGF_{2α} analogs do not decrease IOP by diminishing aqueous humor production. Although the effect on outflow facility has ranged from either no change to a slight increase, this increase does not adequately explain the entire reduction of IOP. Thus increased uveoscleral outflow remains their primary mechanism for lowering IOP. Bimatoprost lowers IOP in normal, ocular hypertensive and glaucomatous eyes.³⁵ It mildly stimulates the rate of aqueous flow by 13 to 14%, but its

ocular hypotensive action is due to a 26% reduction in tonographic resistance to outflow, an increase in the rate of uveoscleral outflow, and/or a lowering in the episcleral venous pressure.

PHARMACOLOGY

Based on similarities in their chemical structures (Fig. 35-1), latanoprost, unoprostone, travoprost, and likely bimatoprost act selectively on the FP receptor, a transmembrane protein similar in structure to rhodopsin. FP receptor linkage with a guanosine triphosphate (GTP)-binding protein results in activation of phospholipase C. This in turn releases intracellular inositol triphosphate and mobilizes intracellular, and possibly extracellular, calcium ions.³⁶ Such

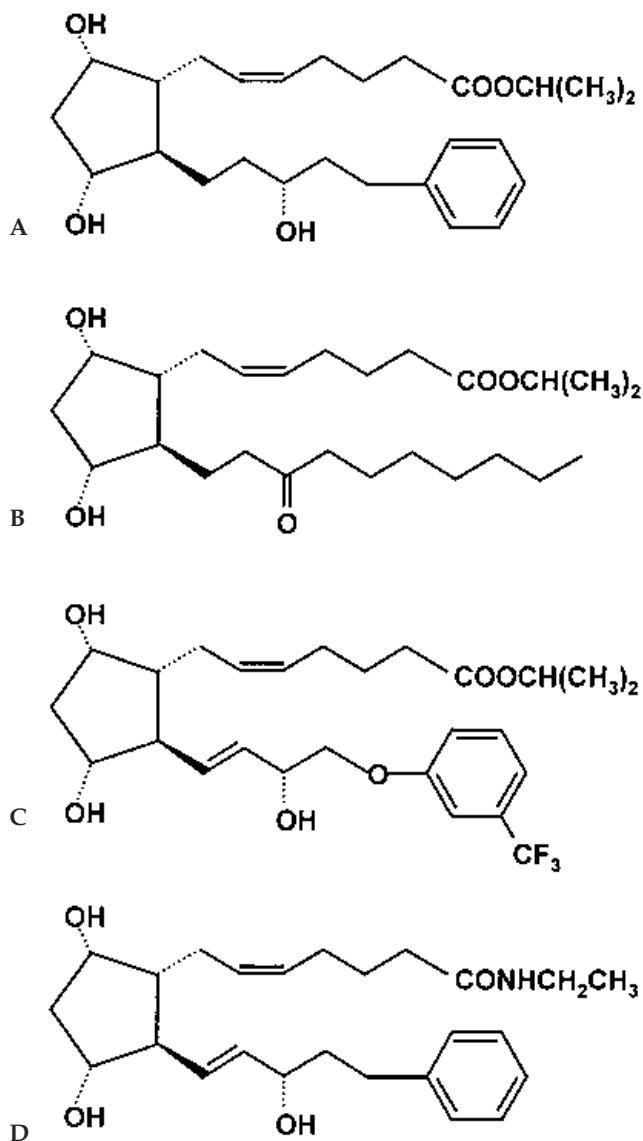


FIGURE 35-1 The chemical structures of prostaglandin analogs that are used clinically in the treatment of glaucoma. (A) Latanoprost. (B) Unoprostone. (C) Travoprost. (D) Bimatoprost.

intracellular changes could hypothetically induce a mechanical or biochemical change in intraocular tissues that some of enhance uveoscleral outflow.

Pharmacologically, some of the PG analogs used to lower IOP share a few important chemical features.³⁷ The 15-hydroxy group is prepared as a racemic mixture of R and S configurations, but the 15 R-epimer is more biologically active and effective for lowering IOP. Substitution of carbons 18 through 20 with a phenyl group allows selective activation of the FP-receptor, which mediates the IOP-lowering effect while minimizing conjunctival hyperemia. Reduction of the double bond at carbons 13 and 14 also diminishes local irritation. For latanoprost, unoprostone and travoprost, the lipophilic isopropyl ester at carbon 1 enhances corneal penetration, whereas corneal enzymes hydrolyze this ester pro-drug to release the active prostanoïd, a free acid. Unoprostone is a pro-drug latanoprost of a metabolite of a PGF_{2α} analog.

Bimatoprost is similar to analog, but has an amide group in place of the isopropyl ester group. The presence of this amide group is responsible for its designation as a prostamide rather than a prostaglandin analog. However, no separate receptor for prostamides have yet been found or characterized biochemically. Cleavage of the amide group to release the free acid has been demonstrated, and is still under investigation. Both bimatoprost and its free acid can bind to FP receptors.³⁸

EFFICACY

Double-masked clinical trials comparing latanoprost 0.005% once daily to timolol 0.5% twice daily in over 800 patients showed that latanoprost reduced IOP by 25 to 35%. This effect was sustained over the full 6-month study period.^{18–20} In patients who continued latanoprost in an unmasked manner, this IOP reduction persisted for 1 to 2 years without tachyphylaxis.^{39–41} Another double-masked study of 184 patients demonstrated similar efficacy after 3 months of treatment,⁴² whereas wash-out studies following chronic therapy showed that this effect could persist for several days to weeks after discontinuation.⁴³

PEARL... PGs have a sustained ocular hypotensive effect that lasts for several days to weeks after discontinuing therapy.

Controlling IOP by increasing uveoscleral outflow offers theoretical advantages over drugs that suppress aqueous humor production. Because the lens and cornea receive nourishment from aqueous humor circulation, reducing aqueous flow could diminish their nutrient supply and increase the concentration of waste products in the anterior chamber. Agents that increase uveoscleral outflow without affecting aqueous flow do not have this disadvantage.⁴⁴

In addition, because PG analogs appear to act differently from most other commercially available glaucoma

drugs, their IOP effects should be highly additive to other agents, particularly those that suppress aqueous humor formation. In a double-masked investigation of patients with IOP greater than 22 mm Hg on either twice-daily 0.5% timolol or 0.006% latanoprost, the addition of the second agent in either group reduced IOP by an additional 15%.⁴⁵ Another study of 50 glaucoma patients treated with timolol showed that 0.006% latanoprost added once daily or twice daily for 12 weeks further reduced IOP by 9 mm Hg (36%) and 7 mm Hg (28%), respectively.⁴⁶

PEARL... Current prostaglandin analogs lower intraocular pressure predominantly by enhancing uveoscleral outflow. This mechanism of action provides excellent additivity when prostaglandins are combined with other glaucoma medications.

The addition of 0.005% latanoprost, once daily, in a double-masked fashion to patients maintained on oral acetazolamide produced a further IOP decrease of 21% following 18 days.⁴⁷ In a study of 22 ocular hypertensive patients using either 0.005% latanoprost or 0.1% dipivefrin, 2 weeks of combination therapy with both drugs yielded total additive IOP reductions of approximately 35%.⁴⁸

The additivity of PGs and pilocarpine appears to be more controversial. Early studies in monkeys demonstrated that pilocarpine blocked the PG-induced IOP-lowering effect of PGF_{2α},^{49,50} supporting the hypothesis that PGs increase uveoscleral outflow. However, in humans, the effects of pilocarpine and latanoprost are additive. Twenty patients with ocular hypertension or open-angle glaucoma were treated with either latanoprost 0.006% twice daily or pilocarpine 2% three times daily for 1 week, at which time the alternate agent was added.⁵¹ The addition of pilocarpine to latanoprost reduced IOP an additional 7%, whereas the other group achieved a 14% further decrease. Overall reduction for these groups was 29 and 27%, respectively. In another study, the addition of a single drop of 0.005% latanoprost to eyes already receiving 0.8% physostigmine every 2 hours for 13 hours produced a significant additive IOP effect compared with placebo.⁵² Thus even very strong miotics can enhance the IOP lowering effect of latanoprost in humans.

SIDE EFFECTS

OCULAR SIDE EFFECTS

Initial studies in human eyes showed that PGs caused burning, stinging, and marked conjunctival hyperemia. Because of this, subsequent development of PG analogs for ocular treatment concentrated on preserving the pressure-lowering effect and minimizing external ocular side effects. During the 6-month trials, the incidence of mild conjunctival hyperemia occurring at least once was 31% in the latanoprost group versus 16% in the timolol group.⁵³ Symptoms

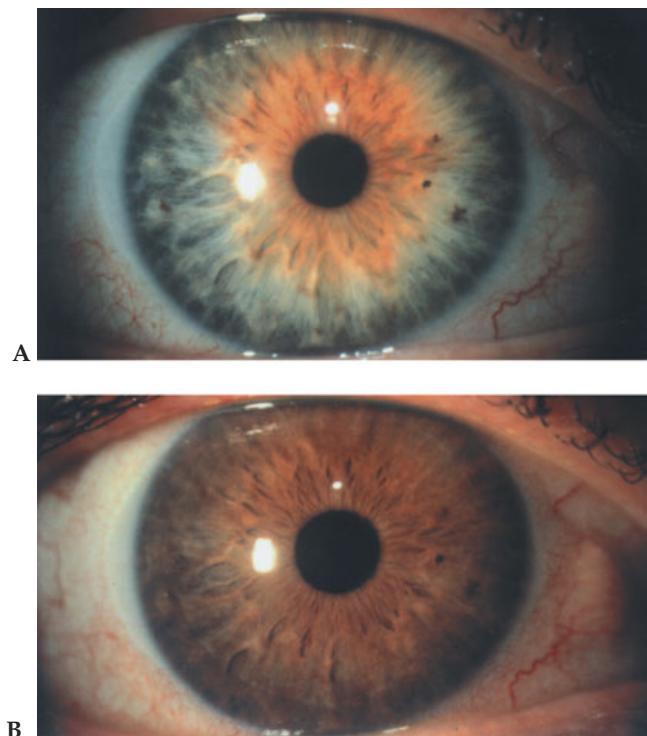


FIGURE 35-2 Effect of latanoprost on iris color. (A) A left eye prior to latanoprost. (B) Same eye, demonstrating marked increase in iris pigmentation following 6 months of latanoprost. (Used with permission from Camras CB, Neely DG, Weiss EL. Latanoprost-induced iris color-darkening, a case report with long-term follow-up. *J Glaucoma* 2000;9:95–98).

of burning, itching, stinging, and tearing were equivalent in both groups. Unoprostone is generally well-tolerated, but it can produce punctate keratopathy.^{54,55}

The well-established ocular side effects of PG administration include an increase in iris pigmentation (Fig. 35-2) and eyelash changes (Fig. 35-3). Increased iris pigmentation primarily develops in patients whose irides are brown

at the pupillary border and hazel to blue more peripherally, with the greatest color change occurring in the relatively hypopigmented peripheral iris (Fig. 35-2). All evidence suggests that this change in color is due solely to an increase in melanin pigment within each melanocyte.^{56,57} There is no evidence that latanoprost causes melanocytes to proliferate. With perhaps rare exceptions, iris pigmentation does not change in patients with uniformly blue or brown irides.^{39–41,57} Latanoprost can also increase the length and pigmentation of eyelashes (Fig. 35-3).^{58,59} These primarily cosmetic changes are most noticeable with monocular use. Recent published experience demonstrates that bimatoprost^{60–64} and travoprost^{65,66} both produce significant increases in both frequency and severity of hyperemia and eyelash growth compared with timolol and latanoprost. Bimatoprost, travoprost, and latanoprost all produce iris color darkening at a similar frequency.

SPECIAL CONSIDERATION

PG analogs darken the iris color and cause eyelash changes in some eyes; neither of these side effects appears to be harmful or vision-threatening.

The initial results of their use in rabbits, as well as the perception of a pro-inflammatory role for PGs in general, has prompted a vigilant search for inflammation and cystoid macular edema (CME) in eyes receiving PGs. However, neither occurred in the approximately 1000 patients who were treated with latanoprost in clinical trials for up to 2 years.^{18–20,39–42}

As orders of magnitude more patients have now been exposed to PG analogs since their commercial introduction, several reports of iritis and CME with latanoprost^{67–71} and the other PG analogs⁷² have surfaced. These include case reports and case series in which some eyes, mostly aphakic and pseudophakic, have developed CME or iritis.



FIGURE 35-3 Effect of latanoprost on eyelashes. (A) The untreated right eye. (B) Latanoprost applied to only the left eye increased length and curliness of eyelashes. These effects are usually easier to detect with unilateral treatment, as in this case. (Courtesy of Julia Whiteside-Michel, M.D.)



B

However, only one report demonstrated a consistent recurrence of moderate iritis upon rechallenge with latanoprost in five eyes of four patients,⁶⁹ and no double-masked challenges with placebo have been conducted. Until we have more experience, PG analogs should be used cautiously or not at all in aphakic and pseudophakic patients with multiple risk factors for CME.^{71,73} Use of a topical nonsteroidal agent in conjunction with these drugs may be considered in these situations.⁷⁴ Similar caution, including careful monitoring with the biomicroscope, is required if used in eyes with a history of uveitis.

CONTROVERSY

Case reports suggest that iritis or cystoid macular edema may be associated with prostaglandin analogs. Although a causal relationship is not proven, care should be taken in prescribing prostaglandin analogs in eyes at risk for these entities.

SYSTEMIC SIDE EFFECTS

Despite a single report of facial rash associated with its use,⁷⁰ it seems unlikely that these agents can cause systemic side effects. The active amount of PG analog applied topically is approximately 1000-fold less than the amount of PGs produced daily in the human body.⁷⁵ Latanoprost has a systemic half-life of 17 minutes, is rapidly converted to an inactive metabolite in the liver, and is excreted primarily in the urine.⁷⁶ The fact that no contralateral IOP-lowering effect was found in clinical trials further supports this lack of systemic action. Latanoprost has also been shown to be safe in patients with moderate, steroid-treated asthma.⁷⁷ Although several vague complaints, such as arthralgias, myalgias, headache, and flulike symptoms were reported in the phase III trials, their overall incidence was similar for both the latanoprost and the timolol treatment groups.^{18-20,42}

PEARL... The systemic side effect profile of prostaglandin analogs appears to be low and will likely remain so, based on pharmacokinetic considerations.

CURRENT FORMULATIONS

ADMINISTRATION

Latanoprost is marketed under the trade name Xalatan as a 0.005% solution and includes 0.02% benzalkonium chloride preservative plus various inert ingredients. Each drop delivers approximately 1.5 µg of latanoprost. Dosing one drop every 24 hours is recommended at bedtime, based on the phase III

Scandinavian trial,²⁰ in which evening administration produced the maximal effect. Though the conventional thought is to minimize cosmetic consequences of hyperemia by evening closing, such as advantage has never been proven. Bimatoprost, 0.03%, is marketed as Lumigan, and 0.004% travoprost is available as Travatan. As with latanoprost, both are administered once daily in the evening. Isopropyl unoprostone, is traded as Rescula at a concentration of 0.15% and recommended administration is twice daily.

COMPARATIVE EFFICACY

Large clinical trials have directly compared 0.005% latanoprost, once daily, to 0.5% timolol, twice daily, in a double-masked fashion for 3 to 6 months.^{18-20,42} The U.S.,¹⁸ Scandinavian,²⁰ and Japanese⁴² trials each showed significantly greater mean diurnal IOP reduction with latanoprost (27–35%) than with timolol (20–27%). In the United Kingdom,¹⁹ timolol reduced IOP by 33% compared with 34% for latanoprost, a difference that was not significant. In a companion study in the United States, 113 patients who completed 6 months of therapy with timolol were switched to latanoprost 0.005% once daily for another 6 months.⁴⁰ Latanoprost further reduced IOP by 1.5 mm Hg, for a total IOP effect 31% greater than the 4.9 mm Hg reduction produced by timolol.

Smaller, short-term studies have compared latanoprost with other IOP reducing agents. In 20 patients, latanoprost 0.006%, twice daily, compared with pilocarpine 2%, three times per day, yielded IOP reductions of 24% and 14% at 1 week, respectively.⁵¹ In another study, twice daily 0.005% latanoprost for 2 weeks reduced IOP by 23%, versus 17% with twice daily 0.1% dipivefrin.⁴⁸

The comparative efficacy of unoprostone, an analog of a PGF_{2 α} metabolite, is less well known.⁷⁸ In glaucomatous monkeys, latanoprost 0.005% lowered IOP more, and for a longer time period, than isopropyl unoprostone 0.12%.⁷⁹ A double-masked trial in patients with open-angle glaucoma or ocular hypertension reported that unoprostone is not as effective as latanoprost.⁸⁰ A large six-month trial found that unoprostone is approximately as effective as betaxolol, but less effective than timolol.⁸¹ Tachyphylaxis to unoprostone has been reported in normotensive volunteers.⁸² Unoprostone received FDA approval as concomitant therapy and is used more as a secondary or adjunctive agent in the treatment of glaucoma.

PEARL... Most prostaglandin analogs, applied once daily, can reduce intraocular pressure more effectively than timolol. Timolol, in turn, is a more effective ocular hypotensive agent than any other class of topical glaucoma therapy.

Recent peer-reviewed publications have compared bimatoprost with timolol⁶⁰⁻⁶² and latanoprost.^{63,64} Others

have studied travoprost versus timolol^{65,66} and latanoprost.⁶⁶ The results of these studies support the conclusions that both bimatoprost and travoprost, used once daily, are more effective than timolol used twice daily and as effective as latanoprost used once daily in terms of their ability to reduce IOP. The relative roles of the various PG agonists in glaucoma therapy await the results of larger, long-term, comparative clinical trials.

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CARBONIC ANHYDRASE INHIBITORS

Ivan Goldberg, M.D.

Derivatives of sulfonamides, carbonic anhydrase inhibitors (CAIs) are the only oral agents available for long-term use in glaucoma. Acetazolamide remains the prototype for the systemic CAIs, which also include methazolamide, dichlorphenamide, and ethoxzolamide. The high prevalence of significant side effects with these agents and potential interactions with other disease processes and drug regimens limits their clinical use and requires thoughtful and knowledgeable prescribing practice.

Over the past few years, dorzolamide and brinzolamide have been developed for topical application. These agents do not carry the same risks as their systemic counterparts, but they are less effective at lowering intraocular pressure (IOP) in most patients. Although occasionally dramatically effective as monotherapy, these topical medications are mainly prescribed adjunctively. Both systemic and topical CAIs are potentially useful inhibitors of aqueous inflow, regardless of the mechanism of raised IOP, and they remain relevant for the treatment of a wide spectrum of glaucoma conditions.

BACKGROUND

Hypothesized as essential for carbon dioxide/bicarbonate metabolism in the 19th century, the enzyme carbonic anhydrase (CA) was first discovered in erythrocytes.¹ It is now evident that the CA enzyme family helps regulate a wide diversity of biological processes, including photosynthesis, cellular and pulmonary respiration, renal tubular acidification, and bone resorption. CA is also critical for maintaining transepithelial fluid transport in the gastrointestinal tract, pancreas, salivary glands, choroid plexus and in the ciliary body, where it plays a key role in aqueous humor formation.

Building on the efforts of Friedenwald, with whom he worked,² and recognizing that CA was necessary for

aqueous production, Becker considered that an inhibitor would reduce IOP.³ Once acetazolamide became available, he reported that oral and intravenous administration in rabbits could reduce aqueous formation by 40 to 50%,⁴ and subsequently described its use in humans.⁵ Several systemic formulations soon became available, generally administered orally. However, wide acceptance of these agents was limited by systemic side effects and the proliferation of effective topical agents from other classes during the 1970s and 1980s.

Initial attempts at topical application of the existing CAIs showed that these were ineffective at lowering IOP, most likely due to poor ocular penetration.⁶ In the early 1980s, subsequent work with compounds modified to enhance water and lipid solubility resulted in the demonstration by Maren and colleagues that topical CAIs could lower IOP in rabbits.^{7,8} Although these initial agents were not tolerated due to local reaction, persistent research eventually led to the development of dorzolamide, which was approved for clinical use in the United States in 1995,⁹ followed shortly by brinzolamide.

MECHANISM OF ACTION

PHARMACOLOGY

CAIs decrease IOP by inhibiting aqueous humor formation (Chapter 3). Inhibition of this enzyme may diminish aqueous humor production by altering the local pH in the nonpigmented epithelium. This could cause a malfunction of enzymes that catalyze ion secretion into the intercellular clefts.¹⁰ The systemic acidosis induced by these drugs may also depress aqueous humor formation.¹¹ However, the extent of inhibition does not highly correlate with systemic acidosis.¹² The observed ocular hypotensive effect of CAIs is probably produced by both local action on the ciliary epithelium and the induced systemic

TABLE 36-1 PHARMACOKINETICS OF CARBONIC ANHYDRASE INHIBITORS⁵⁴

	<i>Acetazolamide</i>	<i>Methazolamide</i>	<i>Dorzolamide</i>	<i>Brinzolamide</i>
Formulation	oral	oral	topical 2% solution	topical 1% suspension
Protein binding	95%	55%	33%	60%
Metabolism	minimal	75%	25–40%	minimal ⁵⁶
Renal excretion	100%	25%	60–75%	75–90% ⁵⁶
Onset	1–2 hours	2–4 hours	1–2 hours	1–2 hours
Peak effect	2–4 hours	6–8 hours	3 hours	2 hours
Duration	6–12 hours	10–18 hours	8–12 hours	8–12 hours
Aqueous flow decrease	20–30% (fluorophotometry)	25% (tonography)	17% (fluorophotometry)	17% (fluorophotometry)
Preservative	N/A	N/A	0.0075% BAC	0.01% BAC
PH	N/A	N/A	5.6	7.5

BAC, benzalkonium chloride.

acidosis. Almost complete enzyme inhibition is needed to achieve a biological effect.

Although at least three CA gene families are known, it is most of the nine isoenzymes of the alpha-CA family that are the targets of CAIs—especially I, II, and IV. CA-II is the predominant isoenzyme in ciliary processes,¹³ although CA-IV, bound mostly to membranes, has also been reported present in the nonpigmented epithelium.

The pharmacokinetics of the currently available agents are summarized in Table 36-1. Although studies report a wide range in the effects of CAIs on aqueous humor production, oral CAIs generally inhibit flow by 20 to 30%. Topical CAIs appear somewhat less effective and usually reduce flow less than 20%. In contrast to beta-blockers, which do not reduce flow during sleep, oral CAIs inhibit nighttime flow by 24%.¹⁴ Because of these apparently different mechanisms of aqueous humor reduction, CAIs can be additive to beta-blockers, producing in some studies an overall reduction that is nearly equal to full additivity of the two agents when used separately.¹⁵

PEARL... Oral carbonic anhydrase inhibitors inhibit aqueous flow by 20 to 30%, whereas the effect of topical CAIs on aqueous flow is generally less than 20%.

As we increase the focus of therapy on the neuropathy of glaucoma, we must also consider the potential effects of topical glaucoma agents on blood flow in the optic nerve head. In this regard, the results from studies of systemic CAIs are mixed.^{16–18} However, dorzolamide has been shown to improve fluorescein flow in the macula and optic nerve head of normal volunteers.¹⁹ In 26 eyes of 26 glaucoma patients, dorzolamide increased peak-systolic central retinal artery velocity, and increased end-diastolic velocity in the ophthalmic and central retinal arteries, with a reduction in the resis-

tance index.²⁰ In addition, both brinzolamide and dorzolamide significantly increased optic nerve head blood flow in rabbits, with minimal systemic acid-base disturbances.²¹ Proof of the benefit of these effects for optic nerve protection in the treatment of chronic glaucoma is eagerly awaited.

SIDE EFFECTS

OCULAR

Although rare, ocular side effects from systemic CAIs include induced myopia or prolonged hypotony following glaucoma drainage surgery. Rarely, CAIs can cause suprachoroidal effusion and angle-closure glaucoma due to anterior rotation of the ciliary body. Ocular side effects from topical agents include surface irritation, dryness or stinging (25%), delayed-onset allergic blepharoconjunctivitis (10%), superficial punctate keratopathy (10%), and, uncommonly, induced myopia. Brinzolamide suspension appears to be more comfortable for the majority of patients than is the dorzolamide solution.²²

SYSTEMIC

Systemic side effects prevent the long-term usage of systemic CAIs in the majority of glaucoma patients, particularly the elderly (Table 36-2). Up to 50% of patients cannot tolerate these agents.^{23–25} All of the commonly used oral CAIs produce similar side effects and IOP reduction when used in equipotent doses. However, individual variations do exist, and one drug may be more tolerable than another, in certain patients.

Initially, an increased urinary loss of sodium, potassium, and bicarbonate results in a modest metabolic acidosis. However, bicarbonate resorption independent of CA permits a new steady state to be achieved, and prevents progressive acidosis.²⁶

TABLE 36-2 SIDE EFFECTS ASSOCIATED WITH ORAL CARBONIC ANHYDRASE INHIBITOR THERAPY

Induced myopia*
Paraesthesiae of fingers, toes, circumoral region*
Decreased dexterity
Leg cramps
Electrolyte disturbances
Metabolic acidosis*
Potassium depletion especially with concomitant diuretics/corticosteroids*
Chloride depletion especially with dichlorphenamide
Uric acid retention
Gastrointestinal upsets
Abdominal cramping/discomfort*
Metallic taste particularly with carbonated beverages*
Anorexia/nausea
Diarrhea or constipation
Weight loss*
Genitourinary problems
Nocturia
Urolithiasis*
Impotence
Frequency with polydipsia (especially in first week of treatment)
Hypersensitivity nephropathy/hepatitis
Central nervous system
Malaise*
Excitement/confusion/insomnia
Fatigue/drowsiness/hearing loss/dyspnea
Headache/irritability*
Vertigo/tremor
Decreased libido
Blood dyscrasias
Thrombocytopenia/agranulocytosis/neutropenia/aplastic anemia*
Hyperchromic anemia
Drug interactions
Interference with anticholinesterase therapy of myasthenia gravis
Exacerbation of bone demineralization effect of diphenylhydantoin
Potentiation of oral hypoglycemic and anticoagulants
Dermatological
Rash (maculopapular)
Pruritus*/flushing
Hirsutism
Exfoliative dermatitis (Stevens-Johnson syndrome)*
Hair loss
Birth defects

*Effects either common or of major clinical concern. (Modified from Stamper RL, Lieberman MF, Drake MV. Carbonic anhydrase inhibitors. In: Stamper RL, Becker B, Shaffer RN, Lieberman MF, Drake MV. *Becker-Shaffer's Diagnosis and Therapy of the Glaucomas*. 7th ed. St. Louis: Mosby; 1999:483–497. With permission.)

Although paraesthesiae occur in two thirds of patients, they do diminish with time. Half of patients note anorexia and weight loss, and 25% report fatigue, malaise, and transient diarrhea. Less-common side effects include confusion, disorientation, nocturia, decreased libido, and depression.

Renal calculi, resulting from diminished excretion of citrate and magnesium and the production of alkaline urine, are 10 to 15 times more common with systemic CAIs.²⁷

Potassium loss may be significant, especially over time and if used in conjunction with other potassium-depleting medications, such as thiazide diuretics and/or steroids. In these cases, serum concentrations must be monitored, although they may not reflect the true situation, as most body potassium is not intravascular. However, unless other problems are present, or patients are on other potassium-sensitive drugs such as digitalis, routine potassium supplements probably are not warranted.

Drug interactions represent another systemic side effect of CAIs, probably secondary to induced acidosis. These include potentiation of the effects of oral hypoglycemics or anticoagulants and partial blockage of anticholinesterases and bronchodilators. In addition, systemic CAIs used with thiazide diuretics can precipitate hyperuricemia. The extent of all of these may be affected by variable drug absorption and patient compliance.^{28,29} As with all glaucoma medications, the patient's primary care physician should be kept informed when these agents are prescribed.

PITFALL... Systemic CAIs can produce a variety of drug interactions, probably secondary to induced acidosis.

Blood dyscrasias and severe skin reactions (Stevens-Johnson syndrome) are rare but life-threatening complications. Thrombocytopenia and agranulocytosis may occur within the first 6 months of initiating therapy, and generally reverse when the drug is stopped. However, aplastic anemia may be idiosyncratic and unrelated to either dose or time of exposure. Pretreatment blood counts, followed by repeat measurements every 2 months for the first 6 months, have been recommended by some authors to detect early, potentially reversible, alterations.³⁰ However, the cost-effectiveness of this approach has been questioned, and this issue remains controversial.^{31,32} At a minimum, patients should be questioned routinely about symptoms of infection and bleeding when treated with chronic oral CAIs. The decreased use of these systemic agents in recent years will diminish the overall incidence of these complications. However, the risk to the individual patient using systemic CAIs today remains the same. Although systemic levels with topical agents are generally lower, rare idiosyncratic hematological reactions remain possible.

CONTROVERSY

Authorities disagree on the value of routinely monitoring blood counts in patients on systemic CAIs. However, at a minimum, patients should be routinely questioned about symptoms of infection and bleeding.

TABLE 36-3 CONTRAINDICATIONS TO ORAL CARBONIC ANHYDRASE INHIBITOR USE

Adrenal insufficiency
Hepatic cirrhosis
Renal failure
Chronic respiratory acidosis
Hyperchloremic alkalosis
Hyponatremia/hypokalemia
Diabetic ketoacidosis
Urolithiasis
Sickle cell disease
Pregnancy/lactation
Special care required with concomitant use of aspirin/corticosteroids

Several strategies can minimize problems from oral CAI therapy. These include starting with a low dose, such as acetazolamide 125 mg twice daily, and advising the patient to take the medication with food. As always, informing the patient about why these medications are necessary and the possible side effects can allay fear and confusion if they occur. Because these drugs generally act quickly, the ocular hypotensive response can be assessed after only a few days, and the dose increased if the IOP reduction is less than desired. If available, methazolamide 100 mg twice daily may be better tolerated than acetazolamide 250 mg four times daily and be equally effective.³³ For children, the pharmacist can crush tablets and suspend them in flavored syrup for a dose of 5 to 10 mg/kg four times daily.³⁴ These agents are generally contraindicated in patients with unstable diabetes; sickle cell anemia; renal, liver, or chronic airways disease; and a history of urolithiasis or sulfonamide hypersensitivity, and in patients who are or may become pregnant (Table 36-3).

Although topically applied, dorzolamide and brinzolamide are systemically absorbed and do bind to erythrocytes.^{35,36} Because serum levels with these topical agents are relatively low, they are capable of reducing IOP without significant effects on electrolyte or acid-base balance. This may also explain their less potent IOP effect.

Systemic effects from the topical agents encompass a metallic taste (in up to 25% of patients), and more rarely, fatigue, urticaria, dizziness, headache, and even depression. Gastrointestinal discomfort may occur, especially in the first few days of use. Aplastic anemia and Stevens-Johnson syndrome of the idiosyncratic variety remain possibilities.

CURRENT FORMULATIONS

ACETAZOLAMIDE (DIAMOX)

The first available CAI, acetazolamide remains the most frequently used oral glaucoma agent. It has been supplied as 125 and 250 mg tablets, and 500 mg sustained release (SR) capsules, although many countries now have access

only to the 250 mg tablets. Effective IOP reduction can be achieved with a dose as low as 62.5 mg twice daily, with maximal benefit seldom achieved by more than 1 gram daily, either as 250 mg tablets q.i.d., or the SR capsules b.i.d. Once-daily SR capsules may be effective throughout the 24-hour cycle for a proportion of patients, and may be better tolerated than the tablets.

500 mg ampules for intravenous use allow dissolution in 5 to 10 mL of sterile distilled water and injection over 5 to 10 minutes. IOP begins to fall within minutes, reaching a peak by 30 minutes, and loss of effect by 4 to 6 hours. Other than intravenous hyperosmotic agents (Chapter 37), this is the fastest and most dramatic method for lowering IOP.

METHAZOLAMIDE (NEPTAZANE)

Supplied in some countries in 25 and 50 mg tablets, dosing of methazolamide ranges from 25 to 100 mg twice daily. More frequent administration is probably not beneficial because it has a plasma half-life of 14 hours. The dose is proportional to both the IOP efficacy and induced side effects, and can be titrated appropriately.³⁷ Because of its pharmacodynamics, methazolamide, 50 mg daily, is probably safer than acetazolamide in patients with renal disease, and it is less likely to produce fatigue, drowsiness, and depression. Methazolamide is much less bound to blood protein, compared with acetazolamide, and is therefore equally effective in smaller quantities.

Dichlorphenamide (Daranide) offers no advantages over acetazolamide or methazolamide, and ethoxzolamide (Cardrase) is no longer available.

DORZOLAMIDE (TRUSOPT)

Marketed as a 2% solution, dorzolamide has been reported with twice-daily instillation to reduce IOP by 21 and 13% at peak and trough times, respectively.³⁸ Dosing t.i.d. improves the trough effect, and this regimen is recommended when this drug is used alone. Longer-term studies have shown that this drug has similar tolerability to betaxolol, timolol, and pilocarpine.^{39,40}

Additive to both other aqueous inflow suppressants (e.g., timolol⁴¹) and outflow enhancers (e.g., pilocarpine⁴⁰), dorzolamide is also available in many countries in a fixed combination with timolol 0.5% (Cosopt, Merck & Company).⁴² Ocular hypotensive efficacy with the fixed combination used b.i.d. is equivalent to that of the two agents used separately but simultaneously.

Because there is much CA in the corneal endothelium, ultrasonic pachymetry has been used to assess possible interference with endothelial function. Conflicting results have been reported: a slight increase in corneal thickness after 4 weeks' application of dorzolamide compared with placebo,⁴³ versus no measurable change after 6 weeks.⁴⁴ Although this is probably not a concern for patients with normal corneas, it may become clinically significant in eyes with compromised endothelial function, such as pre-existing corneal disease or following corneal transplantation.⁴⁵

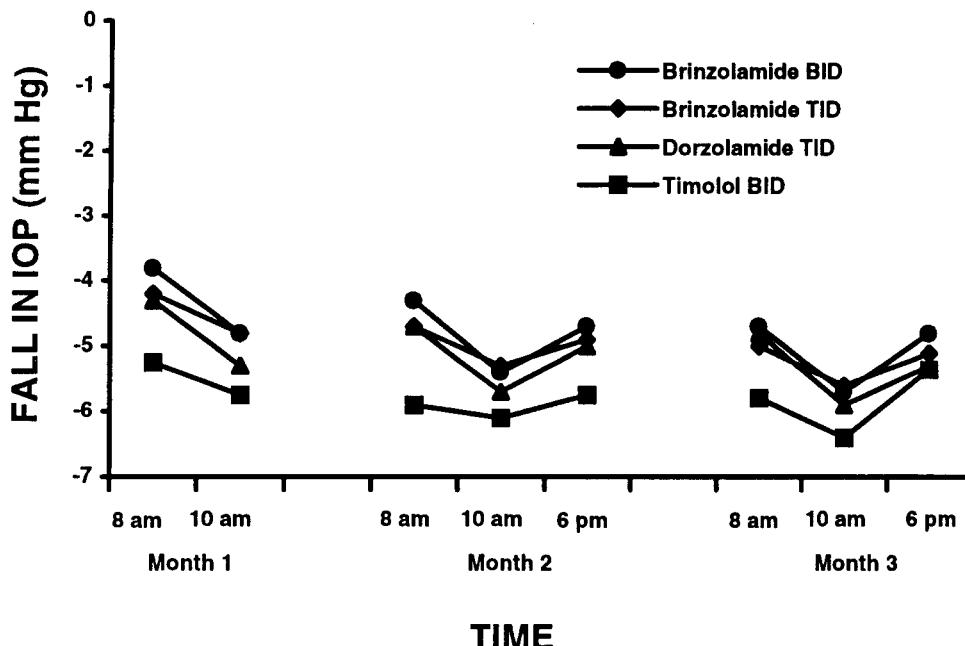


FIGURE 36-1 Ocular hypotensive efficacy of dorzolamide, brinzolamide, and timolol as monotherapy. (Adapted from Silver LH and the Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 1998;126:400–408. With permission.)

BRINZOLAMIDE (AZOPT)

As a 1% suspension, brinzolamide demonstrates good corneal penetration with enhanced ocular hypotensive efficacy, prolonged duration of action, and reduced surface irritation compared with its solution. It is at least as effective as thrice-daily dorzolamide when administered at b.i.d. or t.i.d. frequency,^{40,46} achieving an IOP reduction of between 15 and 22% (Fig. 36-1). About two thirds of patients appear to respond to this agent.

When added to twice-daily timolol maleate 0.5%, brinzolamide lowered IOP a further 13 to 16%.^{47,48} This is statistically equivalent to the adjunctive effect of dorzolamide with timolol. Brinzolamide does not appear to alter either corneal endothelial cell density or corneal thickness in patients with normal corneas over an 18-month period.⁴⁹

CURRENT USAGE OF CARBONIC ANHYDRASE INHIBITORS

GLAUCOMA

Although limited by side effects and overshadowed by other, effective topical agents, oral CAIs retain an important role in the management of several specific glaucoma situations. These include intravenous administration for the rapid reduction of IOP, as already described. This approach may be particularly effective in acute angle-closure glaucoma, allowing laser treatment after reversal of corneal edema, and can similarly permit anterior segment examination and treatment in patients with developmental glaucoma. Other situations where the clinician may wish to consider oral CAIs include patients who are intolerant or incapable of administering topical therapy, or

who are reluctant to undergo laser or surgical treatment. Short-term treatment with oral CAIs can also be considered before and after anterior segment laser procedures, or following ocular surgery, particularly cataract extraction in patients with preexisting glaucoma.

Topical CAIs can be considered for monotherapy in patients in whom beta-blockers are contraindicated, who do not respond well to or have allergic reactions to other medications or are unhappy with the possible side effects to prostaglandin analogs and alpha₂ agonists. With monotherapy, most patients need t.i.d. dosage for an "around the clock" effect. Although a small number of patients will respond dramatically to twice-daily instillations, this needs to be demonstrated by carefully monitoring the IOP. On the other hand, adjunctive topical CAIs may produce adequate additional effects when used b.i.d.

There is no evidence that systemic and topical CAIs are additive to each other. If the IOP reduction of topical preparations is inadequate, and tablets are commenced, the CAI drops should be discontinued.

The major problem with topical CAIs as first-line medical therapy for most patients is their modest hypotensive efficacy and the need for t.i.d. dosing. Their main advantages are their additivity to most other topical agents and their lack of visual side effects and induced adrenergic (and thus potentially vasoconstrictive) tone.

NONGLAUCOMA USES OF CARBONIC ANHYDRASE INHIBITORS

Nonglaucoma ocular uses of CAIs include cystoid macular edema,⁵⁰ (based on the finding that the retinal pigment epithelium is rich in CA), and pigmentary retinal dystrophy, due to a similar postulated mechanism.⁵¹ Nonocular

uses include episodic vertigo, by reducing potassium concentration in the inner ear endolymph and decreasing hair cell excitability,⁵² and high-altitude pulmonary and cerebral edema, or "mountain sickness." In the latter condition, CAIs reduce or eliminate the symptoms of anorexia, nausea, headache, dizziness, fatigue, and weakness caused by reduced arterial oxygen tension by increasing ventilation, increasing alveolar oxygen tension, and reducing serum bicarbonate by inducing metabolic acidosis.⁵³ Finally, by reducing the rate of cerebrospinal fluid formation, systemic CAIs can be used to treat the raised intracranial pressure (ICP) of pseudotumor cerebri and ameliorate a patient's headache, and the real possibility of optic nerve damage from chronic papilledema.

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HYPEROSMOTIC AGENTS

Janet B. Serle, M.D.,
John Danias, M.D., Ph.D., and Donna J. Gagliuso, M.D.

Hyperosmotic agents, administered orally or intravenously, are used to treat acute, substantial elevations of intraocular pressure (IOP) that do not respond to topical ocular hypotensive medications and systemic carbonic anhydrase inhibitors. Because hyperosmotic agents are best tolerated for a limited duration, they are generally used to help control IOP prior to glaucoma surgery, for IOP elevations following surgery or laser procedures, and for pupillary block and ciliary block glaucoma.

Systemically administered hyperosmotic agents are not indicated for the chronic management of glaucoma. The duration of their IOP effect is relatively brief (4 to 6 hours) necessitating frequent dosing. Repetitive use leads to decreased efficacy because the hyperosmotic particles eventually enter the extravascular spaces. Repeat dosage can also increase the incidence and severity of side effects, which range from mildly annoying to significant and even life threatening.

When topically applied, hyperosmotic agents dehydrate the cornea by increasing the osmolarity of the tear film. In this form, these medications improve anterior and posterior segment visualization and are useful diagnostic tools. Long-acting, topically applied hyperosmotic agents can be administered chronically to improve vision in patients with mild corneal edema.

BACKGROUND

Numerous hypertonic substances have been and continue to be used to reduce IOP and to treat cerebral edema. Early hypertonic agents were either ineffective, due to their rapid distribution into total body fluids, or they were too toxic. These included oral sodium chloride and lactose, and intravenous glucose, sodium chloride, sorbital, and gum acacia.^{1,2} In 1956, it was reported that intravenous administration of urea reduced

intracranial pressure.³ Three years later, Galin reported a similar effect on IOP.⁴ Subsequently, mannitol^{5,6} administered intravenously, and oral glycerol⁷ and isosorbide⁸ were all found to effectively reduce IOP (Table 37-1).

MECHANISMS OF ACTION

Hyperosmotic agents reduce IOP through two different mechanisms: (1) a reduction in vitreous volume; and (2) a secondary effect on osmoreceptors in the hypothalamic center of the central nervous system.

Systemic hyperosmotic agents increase the osmolality of the intravascular fluid compared with the extravascular fluid. Because these drugs penetrate very slowly into the avascular vitreous, and the blood–ocular barrier restricts their transport into the eye, this produces an osmotic gradient that draws fluid out of the vitreous into the intravascular space. This loss of fluid shrinks the vitreous and reduces IOP.

Studies in rabbits show that administration of hyperosmotic agents in doses comparable to clinical use reduces vitreous body weight by 3 to 4%.⁹ However, these studies also suggest that a rebound elevation in IOP can occur if the blood–ocular barrier is not intact and hyperosmotic agents enter the intraocular space, or if the osmotic pressure of the dehydrated vitreous becomes greater than the serum osmolality. Either of these situations will encourage movement of fluid from the intravascular space into the vitreous body.

The secondary mechanism, which may have a limited role in IOP reduction, is thought to be mediated through osmoreceptors in the hypothalamic center of the central nervous system. This theory is supported by studies performed in animal models and in patients. Hyperosmotic agents in doses too low to increase serum osmolarity,

TABLE 37-1 COMMERCIALLY AVAILABLE HYPEROSMOTIC AGENTS

Intravenously Administered Agents				
Generic Name	Trade Name	Dosing	Duration of Effect	Side Effects (agent specific)
Urea	Ureaphil	30% solution 2–7 ml/kg	5–6 hours	Local tissue necrosis Thrombophlebitis Transient increase in BUN
Mannitol	Osmotrol	10% or 20% solution 1–1.5 gm/kg	Up to 6 hours	Allergic reaction
Orally Administered Agents				
Generic Name	Trade Name	Dosage	Duration of Action	Side Effects (agent specific)
Glycerol	Osmoglyn	50% solution 1–1.5 g/kg	4–5 hours	Hyperglycemia Glycosuria Caloric load
Isosorbide*	Ismotic	45% solution 1.5–2 g/kg	3½–4½ hours	

*Currently unavailable. BUN, blood urea nitrogen.

administered either orally or intravenously, or injected into the third ventricle of rabbits, were found to reduce IOP in eyes with intact optic nerves.^{10,11} In contrast, similar doses had minimal or no IOP effect in the eyes following unilateral optic nerve transections, suggesting a possible central effect.

PHARMACOLOGY

The ocular osmotic gradient, which governs the IOP reduction, relies on several factors. These include the number of molecules administered (not their size), how rapidly the agent enters the bloodstream, how completely the agent is confined to the extracellular fluid space, how poorly it penetrates into the eye, and how rapidly it is removed by excretion or metabolism.

The greater the number of molecules, the more hypertonic the solution. Thus, substances of lower molecular weight are more effective than similar dosages of substances with higher molecular weight, assuming that all other parameters are equal. Drugs with poor solubility require greater volumes of fluid for administration and are less effective in increasing intravascular osmolality. Because ocular penetration is a function of the permeability of the blood–ocular barrier and the size of the molecule, larger molecules are more effectively kept out of the eye by the blood–ocular barrier. Intravenous administration is the most rapid route for accession of substances into the bloodstream and provides the most rapid onset of action.¹²

PEARL... The ocular osmotic gradient is a function of the number of molecules, not their size.

CLINICAL USES OF HYPEROSMOTIC AGENTS

SYSTEMIC HYPEROSMOTIC AGENTS

Hyperosmotic agents are used to treat acute IOP elevations that do not respond to standard medical therapy (see Table 37-1). They can also be used to acutely increase anterior chamber depth in patients with critically shallow chambers. Clinical indications for hyperosmotic agents include the treatment of acute elevations in IOP prior to filtration surgery, following anterior segment laser surgery, during episodes of pupillary block glaucoma, during an attack of ciliary block glaucoma, and following injection of air or silicone oil during vitreoretinal surgery.

Filtering surgery in an eye with highly elevated IOP can produce a marked, rapid pressure lowering that can result in severe complications such as a suprachoroidal hemorrhage. Hyperosmotic agents, administered intravenously just prior to or at the time of surgery, can reduce the IOP to a safe level prior to opening the eye, reducing the extent of the pressure drop. A hand-held tonometer, such as a Schiøtz, Perkins, pneumatonometer, or Tonopen, can be used to measure IOP in the operating room.

Transient IOP elevations may also occur following intraocular surgery. In this situation, hyperosmotic agents are indicated if topical hypotensive agents and systemic carbonic anhydrase inhibitors are ineffective.

Anterior segment laser surgery can produce clinically significant elevations of IOP in up to 20% of patients that have not been pretreated with ocular hypotensive medications.¹³ In recent years, the use of the alpha-adrenergic agonists apraclonidine (Iopidine) and brimonidine (Alphagan) at the time of laser surgery has considerably decreased the

TABLE 37-2 TOPICALLY ADMINISTERED HYPEROSMOTIC AGENTS

Therapeutic Agents				
Generic Name	Trade Name	Concentration	Duration of Effect	Side Effects
Sodium chloride	Muro 128	5% solution 5% ointment	Up to 7 hours	Occasional mild burning
	Adsorbonac ophthalmic	2%, 5% solution		
	AK-NaCl	5% solution 5% ointment		
Diagnostic Agent				
Generic Name	Trade Name	Concentration	Duration of Effect	Side Effects
Glycerin	Ophthalgan		1–5 minutes	Intense burning

incidence of postlaser IOP spikes and lessened the need for treatment with hyperosmotic agents in this situation.^{14,15} However, these agents are now widely used in the chronic management of glaucoma.^{16,17} Because the chronic use of these drugs may limit their benefit in preventing and treating acute IOP elevations,¹⁸ the need for hyperosmotic agents following laser surgery may once again increase.

Hyperosmotic agents are also used to treat acute IOP elevations in patients with many forms of secondary glaucoma, including neovascular glaucoma and traumatic and uveitic glaucoma. Their short-term use in these situations may help to avoid glaucoma surgery entirely, or at least allow for surgical intervention under more controlled circumstances.

PEARL... Hyperosmotic agents may be used to temporize prior to glaucoma surgery.

Hyperosmotic agents can also help reduce IOP and deepen the anterior chamber in ocular conditions associated with shallowing of the anterior chamber, such as angle-closure glaucoma and ciliary block glaucoma. Because they reduce the vitreous volume, these agents allow the lens and iris to move posteriorly and deepen the anterior chamber. If used before the formation of peripheral anterior synechiae, this effect can also open the anterior chamber angle. However, hyperosmotic agents are not the definitive treatment for these conditions. They should not replace a laser iridotomy for repeat attacks of pupillary block or chronic administration of long-acting cycloplegic agents for patients with ciliary block glaucoma.

TOPICAL HYPEROSMOTIC AGENTS

Topical hyperosmotic agents are often used acutely to dehydrate edematous corneas, which improves examination of the anterior and posterior segments (Table 37-2).

They are particularly useful for performing gonioscopy and diagnosing suspected angle-closure glaucoma in patients with elevated IOP and cloudy corneas.

Used chronically, mild topical hyperosmotic agents can dehydrate corneas with compromised endothelial cell counts. These agents, in the form of drops or ointments, can improve corneal clarity and visual acuity in the early stages of corneal decompensation, often delaying surgical intervention.

SIDE EFFECTS

The majority of side effects from hyperosmotic agents are systemic, some of which can be severe and even life threatening (Table 37-3). These effects, combined with their short duration of action, contraindicate the use of these drugs for chronic glaucoma therapy.

Nausea and vomiting are the most common side effects of hyperosmotic agents, particularly when given orally. Orally administered hyperosmotics must be used cautiously, if at all, immediately prior to surgery.

TABLE 37-3 SIDE EFFECTS OF SYSTEMICALLY ADMINISTERED HYPEROSMOTIC AGENTS

Nausea
Vomiting
Cardiac failure
Headache
Cerebral dehydration
Confusion
Disorientation
Urinary retention
Electrolyte imbalance
Increased diuresis
Subdural hematomas
Thrombophlebitis
Allergy

Systemically administered hyperosmotic agents reduce IOP by causing relative dehydration of the extravascular spaces. This dehydration and the increased intravascular volume are responsible for many of the side effects of these agents. Whereas healthy individuals can tolerate an increased intravascular volume, a systemic hyperosmotic agent can induce acute cardiac failure in patients with chronic congestive heart failure.¹⁹ Headache, a common side effect of hyperosmotic agents, results from cerebral dehydration and reduced intracranial pressure²⁰ and is quite similar to the headache that occurs following lumbar puncture. Cerebral dehydration may also cause confusion and disorientation,²⁰ and both are more common following intravenous administration, due to the rapid onset of their effects.

PEARL... Hyperosmotic agents should be used cautiously, if at all, in patients with reduced cardiac function.

Hyperosmotic agents can also induce diuresis. This results from expansion of the intravascular volume, as well as the urinary excretion of the agents themselves. Anesthetized patients, particularly older men with prostatic hypertrophy, may require catheterization to avoid severe bladder distention.²⁰

Renal failure is another contraindication to the use of hyperosmotics. When used in patients with compromised renal function, these agents may lead to hyponatremia and hypokalemia (because the kidneys are unable to excrete in sufficient quantities the free water that is drawn into the intravascular space by hyperosmotic agents). The resulting imbalance in electrolytes can lead to lethargy, seizures, and coma.²¹ Renal toxicity can follow, as many of the hyperosmotic agents are excreted in the urine, and poor renal function can further compromise their elimination. This situation requires hemodialysis, since neurological deterioration can be rapid.¹⁹

PITFALL... Hyperosmotic agents are contraindicated in patients with renal failure.

Intravenous administration of urea must be carefully monitored, as extravasation during infusion can cause painful, local tissue necrosis.²² Thrombophlebitis has been reported in up to 5% of patients. In contrast, extravasation of mannitol during intravenous administration causes only localized swelling,⁵ and thrombophlebitis is uncommon and very mild, when it does occur.⁶ Other, infrequently reported complications include subdural hematomas with urea²³ and allergic reactions with mannitol.²⁴

CURRENT FORMULATIONS

INTRAVENOUS AGENTS

Intravenous hyperosmotic agents are indicated in patients who are fasting, such as before surgery, and in patients who are nauseated and vomiting. Intravenous agents have a faster onset of action than those administered orally.

Urea

Urea is administered intravenously in a 30% solution at a dosage of 2 to 7 mL/kg. The solution must be freshly prepared because stale solutions decompose to ammonia, a toxic byproduct. IOP reductions occur within 30 to 45 minutes, and peak 1 hour following administration. Persistent reductions in IOP last for 5 to 6 hours.

Because urea is a small molecule,⁶ it is not restricted to the extracellular fluid compartments and moves freely throughout total body water. This makes it less effective than mannitol for reducing IOP in eyes with inflammatory glaucoma and breakdown of the blood–aqueous barrier. Urea is not metabolized and is rapidly excreted by the kidneys.²⁵ The blood urea nitrogen (BUN) level remains elevated for up to 6 hours following administration but returns to normal within 24 hours.²⁶

Mannitol

Mannitol has been used as an ocular hypotensive agent since 1962.⁶ Mannitol is administered as a 10 or 20% solution. Although it is stable in solution, it is soluble only up to a 15% concentration in cold water. If crystals are observed the solution should be warmed and a blood filter used to keep crystals from entering the bloodstream.

The recommended dosage is 1 to 1.5 g/kg of body weight administered at a rate of 3 to 5 mL/min. IOP reductions occur within 30 to 45 minutes, and peak 1 to 2 hours following administration. Persistent IOP reductions have been reported for up to 6 hours.²⁷ Mannitol is not metabolized and is eliminated by the kidneys. Because it is a large molecule, mannitol does not readily cross an intact blood–ocular barrier, and this improves its ability to lower IOP.²⁵

PEARL... Mannitol is the preferred hyperosmotic agent for intravenous administration.

ORAL AGENTS

The advantages of orally administered hyperosmotic agents compared with intravenous agents include more convenient, outpatient administration and less systemic toxicity. However, in addition to the side effects encountered with intravenous administration, oral hyperosmotic agents often produce unpleasant gastrointestinal side effects.

Glycerol

Glycerol, the first clinically useful oral hyperosmotic agent,⁷ is available as a 50% solution in 0.9% saline, which contains 0.62 g of glycerol per mL. The recommended dose is 1 to 1.5 g/kg of body weight. Glycerol is extremely sweet, and it should be given with orange juice or over ice to make it more palatable.

Glycerol is less effective in reducing IOP than intravenously administered hyperosmotic agents. This is due to variable absorption from the gastrointestinal tract and the small size of the molecules, which cross the blood-aqueous barrier relatively easily, particularly in patients with inflamed eyes.²⁶ The onset of the ocular hypotensive effect of glycerol occurs 10 minutes after administration, with the peak effect at 30 minutes to 1 hour. IOP reduction generally lasts for 4 to 5 hours, before returning to baseline.⁷

Glycerol is a component of body fat, constituting approximately 1% of body weight, and it is readily metabolized. In clinical subjects, chronic oral administration and an accidental overdose of glycerol was without side effects.^{21,28} However, glycerol is metabolized to glucose, which can lead to hyperglycemia, glycosuria, and a substantial caloric load in diabetic patients. For these reasons, glycerol is contraindicated in diabetic patients. Because glycerol is metabolized, it has less of a diuretic effect than many of the other hyperosmotic agents.

PITFALL... Glycerol is metabolized to glucose, which can upset glucose control in diabetics.

Isosorbide

Isosorbide was initially used to lower IOP in 1967⁸ and became the oral hyperosmotic of choice in the United States. It is rapidly and almost entirely absorbed from the gastrointestinal tract.²⁹ It is not metabolized, does not cause hyperglycemia, and is excreted primarily by the kidneys.^{30,31} Isosorbide is not as sweet as glycerol and is less likely to produce nausea. Unfortunately, this drug is currently unavailable due to production difficulties.

Ethanol

Historically, ethanol has been evaluated for use as an ocular hypotensive agent in both normal and glaucomatous patients.^{25,32} In sufficiently high doses, ethanol decreases IOP both through a hyperosmotic action and by inhibiting central nervous system secretion of antidiuretic hormone. Intoxication associated with the use of ethanol limits its clinical use as an ocular hypotensive agent.

TOPICAL HYPEROSMOTIC AGENTS

Glycerol

Topically applied glycerol (Ophthalgan, Wyeth-Ayerst) is used to clear corneas with epithelial edema to help establish a diagnosis. This is a particularly useful diagnostic tool in patients with an acute angle-closure glaucoma attack, clearing the cornea sufficiently to permit visualization of the angle by gonioscopy. Whereas the effect of glycerol on the cornea occurs rapidly, within 1 to 2 minutes, its dehydrating effect only lasts 1 to 5 minutes. Several drops of topical anesthetic are required prior to application because glycerol causes intense burning. Topically applied hyperosmotic agents do not reduce IOP.

PEARL... A topical anesthetic must be administered prior to applying glycerol because glycerol causes intense burning when in contact with the nonanesthetized cornea.

Sodium Chloride

Sodium chloride 5% is commercially available as a topical solution and an ointment (Table 37-2). This drug is administered chronically to dehydrate edematous corneas. The ointment formulation can reduce corneal thickness up to 24%. The effect is maximal 3 to 4 hours after application and can last up to 7 hours. Whereas the sodium chloride solution has little effect on corneal thickness,³³ it is less likely to blur vision than the ointment formulation. Side effects are minor, limited to occasional mild burning and irritation.

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Chapter 38

NEUROPROTECTION

Elaine C. Johnson, Sc.D., and John C. Morrison, M.D.

Retinal ganglion cell (RGC) death, loss of axons, and physical changes in the optic nerve head all combine to produce the characteristic cupping of the glaucomatous optic disc. Although efforts to understand the mechanisms of this damage are in progress, it is clear that control of intraocular pressure (IOP) alone, a major risk factor in glaucoma, is not sufficient to preserve vision in all patients. This situation has encouraged broad interest in developing new treatments for glaucoma designed to "protect" the optic nerve directly.

This chapter summarizes the development of the concept of neuroprotection in glaucoma, current progress in the field, and the relationship between IOP lowering

and neuroprotectant therapies. Because development of neuroprotective strategies depends heavily on understanding the mechanisms of glaucomatous optic nerve damage, we also discuss experimental models used to understand these mechanisms.

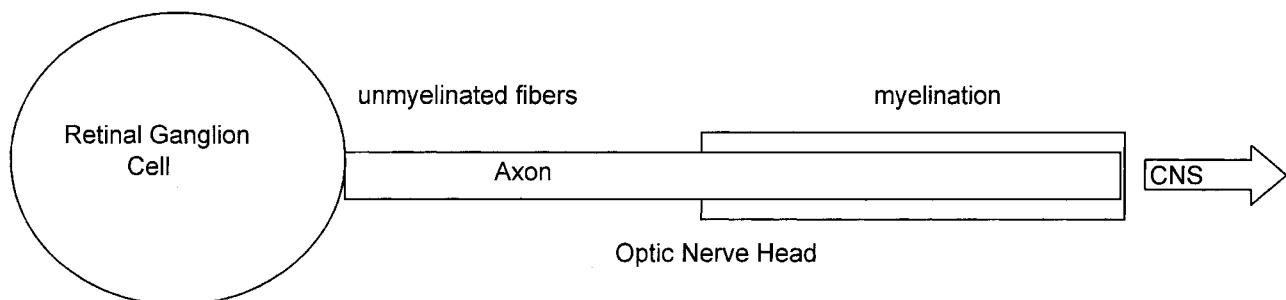
Unfortunately, we still do not understand the precise mechanisms of glaucomatous optic nerve damage. Because of this, many of our concepts for neuroprotection in glaucoma are derived from studies of other neurological problems, such as stroke and various neurodegenerative diseases. This approach has provided many interesting and potentially valuable concepts, which can be divided into three categories (Fig. 38-1). These categories are

RGC Protection

- Inhibition of Injurious Processes:**
- Apoptosis
 - Excitotoxicity
 - Nitric oxide synthase induction**
 - Free radicals and oxidants**

Axon Protection:

- Regulation of intracellular calcium
- Calpain inhibition



Enhancement of Endogenous Neuroprotection:

- Neurotrophic support
- Heat shock proteins
- Adenosine
- Glutathione**

*Processes which may affect both the retinal ganglion cell and the axon.

FIGURE 38-1 Potential strategies for neuroprotection in glaucoma include (1) protect the RGC by inhibiting processes that might injure it, (2) enhance endogenous RGC survival mechanisms, and (3) protect the optic nerve axons.

neuroprotective strategies designed to (1) protect the RGC from the effects of the release of injurious molecules, (2) enhance endogenous RGC survival mechanisms, and (3) protect optic nerve axons. To help the reader continue to evaluate progress in the development of potential neuroprotectants, we conclude this chapter with several guidelines for assessing the value of future studies in this important and rapidly evolving field.

BACKGROUND

The concept of neuroprotection emerged in the 1980s, when Olney and others showed that a number of glutamate receptor antagonists could limit neuronal loss in the brain and retina after acute ischemia and subsequent reperfusion.^{1,2} Since then, this field has expanded into a vigorous and extensive search for other potential therapeutic agents that might protect neurons in such diverse neurodegenerative diseases as Alzheimer's, Parkinson's, and diabetic neuropathy. In the eye, neuroprotective agents have been suggested as therapies for photoreceptor degeneration, macular degeneration, retinal ischemia, and glaucoma.

Currently, elevated IOP is the best-recognized risk factor in glaucoma, and reduction of IOP by pharmacological or surgical therapy can effectively preserve axons and visual function in many individuals.^{3–5a} In this sense, lowering IOP in many individuals with glaucoma is itself neuroprotective,⁶ and it seems unlikely that any neuroprotective therapy will be totally effective in the face of uncontrolled, elevated IOP. Because of this, enthusiasm for identifying new, neuroprotective therapies should not obscure the importance of IOP reduction.

However, problems with compliance, side effects from pressure-lowering medications, and potential complications from glaucoma surgery can limit the effectiveness of lowering IOP in some patients. In addition, relentless, progressive visual-field loss can occur in some patients whose IOP is well controlled by therapy.^{3,4} It seems likely that, in these individuals, injurious events initially set in motion by the elevated IOP continue long after it is controlled. Similarly, additional lowering of IOP may not stabilize all glaucoma patients who have normal pressure and progressive field loss. For these reasons, pressure-lowering strategies augmented by neuroprotective therapy may be the most effective approach for preventing glaucomatous vision loss.

SPECIAL CONSIDERATION

Pressure-lowering strategies augmented by neuroprotective therapy may be the most effective approach for preventing glaucomatous vision loss.

Effective neuroprotection in any setting is currently an unrealized therapeutic goal, and not yet an established clinical reality.⁷ For glaucoma, current and future neuroprotective strategies will depend on proven or hypothetical understanding of the mechanisms of axonal injury and RGC death in this disease. Specific, effective neuroprotectant strategies that are tailored to the unique pathophysiology of glaucoma and anatomy of the retina and optic nerve head require detailed understanding of the mechanisms of glaucomatous optic nerve damage. This understanding will rely on observations of the pathology of glaucoma and on the experimental manipulation of known glaucoma genes⁸ and risk factors (e.g., IOP).

In the absence of this knowledge, many of our current ideas on neuroprotection are now borrowed from our understanding of the injury processes and neuroprotectant strategies for other neurodegenerative diseases, and then applied to the problem of preventing glaucomatous injury. This approach will undoubtedly provide additional classes of potential neuroprotectants, which can then be tested using relevant models of glaucomatous optic nerve damage. These experiments will not only determine the value of these potential therapies, they may also improve our understanding of the mechanisms of the optic nerve damage itself.

UNDERSTANDING THE MECHANISMS OF GLAUCOMATOUS OPTIC NERVE DAMAGE

As already mentioned, understanding the basic mechanisms of glaucomatous optic nerve damage is essential for developing effective neuroprotective strategies. This understanding depends on both the pathology of the glaucoma and the careful study of relevant animal models in which hypotheses can be tested. The basic pathology of glaucomatous optic nerve damage is summarized in Chapter 10.

EXPERIMENTAL MODELS TO EVALUATE NEUROPROTECTION

Retinal ischemia and optic nerve transection are two common experimental animal model systems used to evaluate the response of RGC to injury. Retinal ischemia is usually induced in rats by short-term exposure to elevated IOP that is sufficient to produce retinal and choroidal vascular occlusion, usually greater than 100 mm Hg for at least an hour. This ischemic period is followed by reperfusion, during which additional injurious processes occur in the tissue. Ischemia generally results in delayed thinning of the inner retina and RGC apoptosis.⁹ The relevance of such models for studying neuroprotection in glaucoma depends on the role of ischemia in glaucomatous injury.

Optic nerve transection produces characteristic responses of the RGCs and proximal axons that vary with the location and completeness (complete axotomy, crush, or partial crush) of the injury.¹⁰ Following intraorbital optic nerve transection near to the globe, RGC death is

delayed for about 1 week, offering an opportunity to test potential neuroprotectants. The duration of RGC survival increases as the distance between the cell body and the transection site increases. By contrast, an optic nerve crush is used to retain the organization of the connective and glial components of the nerve which, in peripheral nerve, enhance regeneration.

In general, transection or crush of the optic nerve, without injury to the vasculature, will produce injury confined to the RGC layer of the retina. Because of the apparently specific loss of RGCs in glaucomatous injury, these models are useful for studying the cellular processes of retinal ganglion cell death. However, the mechanism of the injury to the RGC and their axons in these models may be significantly different from that which occurs in glaucoma, which most likely primarily occurs in the unmyelinated optic nerve head (Chapter 10).

Models using elevated IOP may more closely replicate human glaucomatous pathology. In primates, laser photocoagulation of the trabecular meshwork increases resistance to aqueous humor outflow and elevated IOP.^{11–13} The resulting optic nerve and retinal damage bears several similarities to human glaucoma. Unfortunately, cost and availability limit the use of these rare animals for detailed studies of the mechanism of optic nerve damage and testing potential neuroprotectants. Although models of chronically elevated IOP have been described in rabbits, the unique characteristics of the optic nerve head in these animals may diminish their relevance to human glaucoma.

Recently, elevated IOP has been produced in rats by either episcleral vein sclerosis, vein cauterization, or laser photocoagulation.^{14–16} The development of such rodent glaucoma models potentially allows the economical testing of neuroprotectants in a more realistic, *in vivo* situation, using numbers of animals sufficient to overcome unavoidable differences between animals.

POTENTIAL MECHANISMS OF GLAUCOMATOUS NEUROPATHY: PRELIMINARY IDEAS

In spite of these efforts, we still know very little about the mechanism of glaucomatous optic nerve damage. Because of this, we are limited to looking for “likely players,” as suggested by related studies in stroke, trauma, and various neurodegenerative diseases.¹⁷

In recent years, investigators have proposed several mechanisms of neural injury that may play a role in glaucoma. For most of these, potential therapeutic agents exist and some preliminary studies have been reported with these drugs. In general, these mechanisms concern either direct RGC injury or primary injury to the RGC axon (Fig. 38–1). Neuroprotection against RGC injury, which will be considered first, can be directed either against processes that injure RGCs, or toward enhancing the effectiveness of preexisting

endogenous neuroprotective mechanisms. Neuroprotection against axonal damage focuses on calcium entry and its effects on the cytoskeleton, as well as on enhancing axonal survival and regeneration following the injury.

NEUROPROTECTION TARGETED TO RETINAL GANGLION CELL SURVIVAL AND FUNCTION: PROTECTION AGAINST INJURIOUS PROCESSES

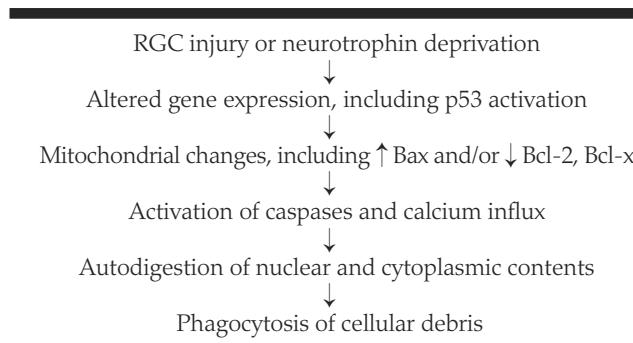
APOPTOTIC PROCESSES: NEUROPROTECTION TO INHIBIT PROGRAMMED CELL DEATH

Apoptosis, also called programmed cell death, is a controlled form of cellular “suicide,” in which the nucleus and cytoplasm are autodigested and the cell fragmented into pyknotic bodies, which are then phagocytosed by surrounding cells. The alternative to apoptosis is necrotic cell death, which allows the uncontrolled release of proteolytic enzymes and injurious molecules from the dying cell. In contrast to necrosis, apoptosis minimizes inflammation and further injury to the tissue. Apoptosis is a genetically conserved process that is very important in development and the regulation of normal tissue turnover. Because it is dependent on new protein synthesis, apoptosis can be blocked by protein synthesis inhibitors.

RGC apoptosis is the culminating event in an expanding cascade of biochemical responses (Table 38–1).^{18–22} These include the sustained expression of transcription factors, activation of a tumor suppressor protein p53, alterations in the Bcl-2:Bax equilibrium, the activation of a family of cysteine proteins called caspases and uptake of calcium by mitochondria. While Bax and p53 encourage apoptosis, Bcl-2 inhibits this process. Caspases are enzymes with a broad spectrum of proteolytic activities, which includes the degradation of DNA repair enzymes and cytoskeletal proteins, such as actin. Further clarification of the steps in these pathways that lead to RGC apoptosis, including their activators and inhibitors, may yield new opportunities to modify this process.

RGC death by apoptosis follows optic nerve transection in both primates and rats^{23–25} and in retinal ischemia models.^{9,26} RGC apoptosis has also been identified in

TABLE 38–1 A SIMPLIFIED APOPTOTIC PATHWAY



human glaucoma specimens²⁷ as well as in primate, rabbit, and rat retinas following moderate, experimental elevation of IOP.^{23,28}

The recognition that RGCs die by apoptotic mechanisms in glaucoma has led to the hope that agents that inhibit this process might be used therapeutically in glaucoma.^{22,23,29,30} One such approach would be to alter the expression of genes that regulate the apoptotic pathway, such as overexpression of the anti-apoptotic protein BCL-2.^{31,32} However, this system is likely quite complex, and such manipulations can produce unexpected results.³³

A potential shortcoming of anti-apoptotic therapies for neuroprotection in glaucoma is that they do not inhibit the underlying injurious processes. As these processes continue, their downstream effects may overwhelm any anti-apoptotic therapy and merely delay ultimate cell death.³⁴ Similarly, uncontrolled cell death from necrosis may also occur.

SPECIAL CONSIDERATION

Although therapies designed to limit retinal ganglion cell apoptosis in glaucoma may theoretically improve RGC survival, they do not address the underlying injurious processes.

THE INFLUENCE OF ISCHEMIA STUDIES ON THEORIES OF NEUROPROTECTION FOR GLAUCOMA

The retinal ischemia model has supplied several theories of the mechanism of RGC loss in glaucoma. Ischemic insults to the retina, as well as other areas of the central nervous system, result in necrotic and apoptotic neuronal loss, release of excitatory amino acids (excitotoxicity), production of oxygen free radicals (oxidative injury), and disrupted calcium homeostasis (Table 38–2).³⁵ Such studies

TABLE 38-2 POTENTIAL MECHANISMS OF INJURY FOLLOWING ISCHEMIA

Ischemia
↓
Depleted energy stores
↓
Membrane depolarization
↑ Intracellular calcium and glutamate release
Reperfusion
↓
Glutamate receptor overstimulation and excitotoxicity
↓
Further depolarization
↑ Nitric oxide and oxidative damage
Protease activation

have led to the development of many therapeutic agents that can rescue neurons that would otherwise have died as a delayed result of the injury.

These injurious processes also occur following optic nerve injury.^{10,36–39} Some of the same neuroprotective agents used in ischemia can rescue axotomized RGCs.^{40–43} Agents that protect against ischemia may also be neuroprotective in glaucoma.⁴⁴

NEUROPROTECTION AGAINST EXCITOTOXIC MECHANISMS IN GLAUCOMA

Excitotoxicity describes a secondary neural injury following acute ischemia or other insults that result in uncontrolled release of excitatory neurotransmitters, principally glutamate and aspartate, coupled with failure or reversal of their energy-dependent uptake systems.^{1,45,46} Elevated extracellular glutamate results in prolonged overstimulation of excitatory receptors, leading to increased levels of intracellular Na⁺, Ca⁺⁺, and Cl⁻. These alterations activate proteases, uncouple oxidative phosphorylation, and release reactive oxygen species. These processes can also result in neuronal death outside the area originally affected by the ischemic injury.

Evidence for this mechanism of neural injury does not depend entirely on the measurement of increases in extracellular excitatory amino acids. Instead, it has been found that agents that block excitatory neurotransmitter receptors are capable of limiting the size of ischemic lesions, and application of receptor agonists can reproduce the pathology seen in ischemic tissue.

Pharmacological studies of glutamate excitotoxicity have revealed distinct types of glutamate receptors: N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate, and guary into a XXXXXXX about word. The neuroprotective effect of antagonists for each of these receptor types will depend upon the relative contribution of its overactivation to cell damage and death in glaucoma.

Investigators have described NMDA receptors on RGCs⁴⁷ as well as other glutamate receptor types in the inner retina and optic nerve. Additionally, NMDA excitotoxic injury produces a selective loss in RGCs, much like that seen in glaucoma.^{48,49} This similarity suggested that excitotoxicity might play a role in human glaucoma. Indeed, elevated glutamate levels have been found in vitreous samples from both human and experimental glaucoma eyes,⁵⁰ although more recent work in experimental monkey glaucoma does not support this finding.^{50a} Moderate experimental elevation of glutamate can result in selective ganglion cell loss.⁵¹

Glutamate receptor antagonists, such as the NMDA channel blocker, MK-801, appear to protect RGCs from both ischemia and elevated IOP.^{52,53} Memantine, an NMDA receptor antagonist, has been shown to decrease RGC loss from intravitreally injected glutamate and is

currently being investigated in a large multicenter study of glaucoma patients.⁵¹ However, the excitotoxicity hypothesis in itself does not explain all aspects of glaucomatous optic nerve damage, such as why RGCs in some regions are apparently more easily damaged than in others.

SPECIAL CONSIDERATION

Despite its appeal, the excitotoxicity hypothesis does not currently explain regional variations in retinal ganglion cell susceptibility, as reflected in the characteristic patterns of glaucomatous visual-field loss.

NEUROPROTECTION AGAINST NITRIC OXIDE SYNTHASE INDUCTION AND NITRIC OXIDE IN GLAUCOMA

High levels of the transmitter, nitric oxide, produced by nitric oxide synthase (NOS), can also precipitate neural injury. Ischemia and reperfusion, overstimulation of glutamate ionotropic receptors, and increased levels of intracellular calcium can all induce NOS. This induction appears to inhibit ion channel adenosinetriphosphatases (ATPases) and the glutamate transporter, and encourages synthesis of apoptotic proteins.⁵⁴ Therefore, NOS induction may play a key role in both excitotoxic injury and the induction of apoptosis. In support of this, optic nerve transection results in NOS induction in the retina, and intravitreal injection of NOS inhibitors enhances the survival of RGCs.⁵⁵

Neufeld et al have shown that NOS isoforms are present in the human optic nerve head and may be selectively increased in glaucoma.⁵⁶ They reported that a selective inhibitor of inducible NOS, aminoguanidine, can reduce RGC loss in rats with experimentally elevated IOP, suggesting that this agent may have neuroprotective potential.⁵⁷ However, constitutive NOS isoforms can actually be neuroprotective following retinal ischemia, and some NOS inhibitors can increase retinal damage.⁵⁸ Therefore, potential neuroprotectants based on NOS inhibition must be selective for the injurious effects of NOS and spare those that are protective.

SPECIAL CONSIDERATION

Injury due to nitric oxide synthase induction may occur both in the retina and in the optic nerve head, and NOS inhibition may be neuroprotective in both regions. However, it is unclear how induction of NOS could lead to the specific patterns of nerve fiber loss seen in glaucoma.

NEUROPROTECTION TARGETED TO RETINAL GANGLION CELL SURVIVAL AND FUNCTION: ENHANCEMENT OF ENDOGENOUS NEUROPROTECTIVE MECHANISMS

The normal optic nerve and retinal tissues possess several potentially protective processes that may act against glaucomatous optic nerve injury. These include the retrograde transport of neurotrophins to the ganglion cells, which depend on these growth factors to maintain normal function. Other endogenous potential neuroprotectants include heat shock proteins, glutathione, and adenosine. Enhancing these endogenous mechanisms offers an attractive approach to neuroprotection because this relies on the natural functions that may have been altered by the glaucomatous process and may address some of the underlying mechanisms of nerve damage.

NEUROPROTECTION BY ENHANCING NEUROTROPHIC SUPPORT TO RETINAL GANGLION CELLS

During development, many neurons fail to establish synaptic contact with appropriate target tissues. These neurons die by apoptotic mechanisms. Neurotrophins, including the nerve growth factor (NGF) family of proteins, are produced in limited quantities by the target tissues of these neurons. They are able to rescue developing neurons from apoptosis in vitro studies and, when added exogenously, promote neuronal survival in vivo.

The NGF family of neurotrophins interact with a group of related, high-affinity receptors, resulting in the activation of intrinsic tyrosine kinases (Trk), as well as a low-affinity receptor, p75.⁵⁹ The retrograde transport of activated neurotrophin-Trk complexes to the RGC nucleus produces a cascade of signal transduction responses, affecting the expression of numerous key genes.⁶⁰

Adult neurons can also respond to neurotrophins. In the adult animal, neurotrophins are produced by neuronal target tissues, glial cells,^{61,62} and the neurons themselves.⁶³ Recognition of the powerful neuroprotective effects of neurotrophins during development has prompted great interest in understanding the roles of these substances in the adult nervous system.

Several neurotrophins appear to exert trophic influences on both developing and adult RGCs (Table 38–3).^{64–68} In addition, the BDNF and NT4/5 high-affinity neurotrophin receptor, Trk B, and the low-affinity receptor p75, have both been identified in RGCs.^{59,69,70}

Many of these neurotrophins delay RGC apoptosis.^{66,68,71–75} So far, however, neurotrophin rescue of RGCs appears temporary,^{76,77} leading to the suggestion that

TABLE 38-3 RETINAL GANGLION CELL NEUROTROPHINS AND THEIR RECEPTORS

Brain Derived Neurotrophic Factor (BDNF)	TrkB, p75
Neurotrophin 4/5 (NT 4/5)	TrkB, p75
Ciliary neurotrophic factor (CNTF)	CNTF Receptor
Basic fibroblast growth factor (bFGF)	FGF Receptor-1
Glial derived neurotrophic factor (GDNF)	GDNF Receptor

other factors, including a reduction in the amount of Trk receptors, may play a role in eventual RGC death. In fact, retrograde delivery of Trk genes has produced extended survival of RGCs following optic nerve transection.⁷⁸

Elevated IOP results in obstruction of bidirectional axonal transport at the optic nerve head.^{79–80} This reduces delivery of proteins synthesized by the RGC to the axon and synapse and diminishes the supply of target-derived neurotrophins to the cell body (Fig. 38-2).⁸¹ Because RGC health and function may depend on neurotrophins derived from its target tissues, elevated IOP in glaucoma might reduce neurotrophic support of RGCs, resulting in compromised RGC function and eventual apoptotic cell death.

The neurotrophin depletion theory of RGC loss in glaucoma is appealing because it explains how retrograde transport obstruction at the optic nerve head could result in the selective patterns of RGC and axonal loss observed in glaucoma (Chapter 10). However, if axonal injury at the optic nerve head results in axonal degeneration, rescue of axotomized RGCs by neurotrophin delivery does not solve the formidable problems of axonal regeneration, pathfinding, and the reestablishment of functional connections.^{82,83} Preserving the RGC may not successfully preserve visual function.

SPECIAL CONSIDERATION

The neurotrophin depletion theory of glaucomatous retinal ganglion cell loss ties together observations of altered retrograde transport in glaucoma and the characteristic pattern of axonal loss and visual field damage. However, rescue of retinal ganglion cells alone may not enhance or preserve visual function.

NEUROPROTECTION OF RETINAL GANGLION CELLS BY OTHER ENDOGENOUS MECHANISMS

Heat shock proteins are expressed after many types of neural injury, including hyperthermia, ischemia, and excitotoxicity.⁸⁴ They act as molecular chaperones, aiding in the refolding of denatured proteins and protecting them from degradation. These proteins are induced in the retina following ischemia,⁸⁵ and their presence appears to provide resistance to ischemia and to excitotoxicity to RGCs in vitro.⁸⁶

Naturally occurring RGC death during development can be regulated by the availability of the antioxidant glutathione, and exogenous glutathione can prevent excitotoxic RGC death in vitro.⁸⁷ Other antioxidants may also provide neuroprotection, and deserve careful analysis for the treatment of glaucoma.

Adenosine, an inhibitory neuromodulator, is released in ischemia and appears to counteract many of its injurious processes.⁸⁸ This is a critical component in the phenomenon of tolerance, whereby brief periods of ischemia provide protection against subsequent ischemic episodes.⁸⁹ This protective function appears to result from adenosine's ability to counteract neuronal calcium influx, inhibit microglial activities, and stabilize differentiated astrocytic functions.⁹⁰ These same properties may also protect axons, such as

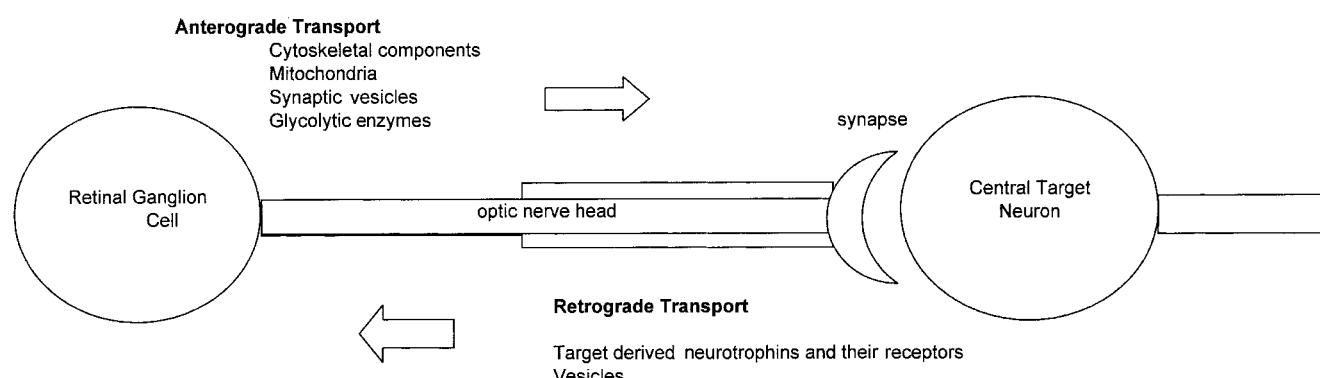


FIGURE 38-2 Schematic representation of axonal transport. Obstruction of axon transport at the optic nerve head decreases anterograde delivery of axonal and synaptic components to the optic nerve axons and diminishes the retrograde supply of target-derived neurotrophins and vesicles to the retinal ganglion cell. This latter effect may affect the production of proteins vital to the continued function of the retinal ganglion cell and lead to eventual cell death by apoptosis.

those of the optic nerve.^{91,92} Experiments with pharmacological adenosine receptor agonists show that these compounds can offer neuroprotection in neurodegenerative diseases as well as acute cerebral and retinal ischemia.^{93–97}

NEUROPROTECTION TARGETED TO AXONAL SURVIVAL AND FUNCTION

Although not proven, the optic nerve head has long been considered the primary site of axonal injury from elevated IOP, with subsequent physical and biochemical events contributing to progressive axonal loss.⁹⁸ Experimental studies have shown that elevated IOP obstructs axonal transport at the level of the lamina cribrosa,^{79,80} and suggest that this obstruction is accompanied by depleted neurotrophins and loss of astrocytic gap junctional communication.⁸¹ Little is known about how these and other events result in axonal degeneration, but loss of axonal membrane (axolemma) integrity may be a crucial step in this process.

PEARL... It is very likely that, in glaucoma patients with progressive field loss despite controlled intraocular pressure, a loss of axonal function may precede actual axon degeneration and retinal ganglion cell death. Therefore, rescuing axons from the events set in motion by elevated intraocular pressure is an important goal of neuroprotection.

Studies of isolated axons demonstrate that loss of the action potential is an early response to reduced axolemmal integrity. It is followed by reversible alterations in mitochondria and transport, and, finally, irreversible structural disintegration and conduction block (Table 38-4).⁹⁹ Because loss of physiological function, interruption of axonal transport, and changes in mitochondria all appear to be reversible, this offers a window of opportunity for repair and recovery. This section discusses agents with the potential to protect optic nerve axons. These include calcium channel inhibitors and calpain inhibitors.

TABLE 38-4 SEQUENCE OF AXONAL RESPONSES TO INJURY (BASED ON STUDIES OF ELECTROPORATION IN THE SQUID GIANT AXON⁹⁹)

1. Temporary loss of action potential.
2. Swollen mitochondria and reduction in their transport rate.
3. Sustained action potential loss, swollen organelles, cessation of mitochondrial transport, and reduction in the transport of other organelles. *These alterations can be reversed if the nerve is temporarily placed in a medium that resembles the intracellular milieu immediately after poration. This reversal is sustained when the axon is reexposed to the normal extracellular-type medium.*
4. Clumping or liquification of the axoplasm. *This is not reversible.*

NEUROPROTECTION: INCREASED INTRACELLULAR CALCIUM LEVELS AND AXONAL INJURY

During ischemia, optic nerve injury depends on the entry of calcium into the cell from the extracellular space.^{100–101} Increased intracellular calcium activates endonucleases, protein kinases, calpains, phospholipases, and NOS. These, in turn, lead to degradation of DNA and cytoskeletal proteins and the generation of free radicals.^{102,103} Because of this, neuroprotective strategies may also include controlling the influx of calcium.

Optic nerve ischemia studies demonstrate that axonal mitochondrial calcium increases greatly when anoxia is followed by reperfusion.^{104–105} Optic nerve axons have L-type and N-type high-voltage channels, as well as a sodium calcium exchanger.^{106,107} Shortly after axotomy, calcium levels appear to increase within axonal mitochondria and in areas where cytoskeletal proteins are disintegrating.¹⁰⁸ Therefore, agents that prevent increases in intracellular calcium may be used therapeutically to protect axons.

Calcium channel blockers, such as verapamil, nimodipine, and nifedipine, are used as antihypertensive agents and cerebral vasodilators and to treat coronary heart disease. Some clinical studies suggest that these agents may reduce visual field loss progression in normal tension glaucoma, possibly by improving retrobulbar perfusion,¹⁰⁹ although their effect on primary open-angle glaucoma is equivocal (Chapter 15).^{110–117}

NEUROPROTECTION TO INHIBIT PROCESSES SET IN MOTION BY INCREASED CALCIUM LEVELS IN THE AXON

Increased intra-axonal calcium leads to rapid activation of calpain, a protease with specificity for axolemmal and cytoskeletal proteins such as spectrin, fodrin, and neurofilaments.^{118–120} Inhibition of calpain has been proposed as a neuroprotectant strategy following ischemia,¹²¹ and calpain inhibitors have shown neuroprotective potential in brain ischemia.^{122,123} In addition, calpain inhibition can limit degradation of neurofilaments following traumatic injury to the brain^{124,125} and spinal cord.^{120,126} Clearly, the diverse effects of calpain must be better understood before we can realize the full potential of calpain inhibition as a neuroprotective strategy.

GUIDELINES FOR EVALUATING NEUROPROTECTION STUDIES

As more glaucoma neuroprotection literature appears, the guidelines listed in Table 38-5 should assist the reader in evaluating their promise as therapeutic neuroprotectants in glaucoma. The following comments amplify several of the points made in the table.

TABLE 38-5 CONSIDERATIONS FOR EXTRAPOLATING EXPERIMENTAL NEUROPROTECTANT STUDIES TO POTENTIAL HUMAN GLAUCOMA THERAPY

In vitro or in vivo

If original observations are from in vitro studies, have they been extended to relevant animal models? If an animal model is used, what are the important anatomical differences between the model and the human eye?

Injury model used

What attempts are made in the experimental design to mimic the known pathological events that occur in glaucoma? For example, age is an important risk factor in glaucoma. Do the conditions in which neuroprotection is evaluated accurately reflect those known to exist in aged animals or humans? This is especially relevant if the study uses embryonic or neonatal models, but may also be important if very young, adult animals are used.

Mechanism of injury

When protection against a specific mechanism of injury is proposed, how good is the evidence that such processes actually occur in human or experimental glaucoma?

Severity of injury

Is the experimental manipulation reasonable? For example, how do the intraocular pressure levels reached compare with those experienced in human glaucoma? How accurately does acute optic nerve transection mimic the gradual loss of axons over months, let alone decades?

End point

Does the experimental end point indicate preserved or restored physiological function? Retinal ganglion cell survival and axonal sprouting alone are not necessarily the same as functional recovery.

Neuroprotection duration

Is the protection temporary or long lasting? Has an effort been made to determine the time course of the protection?

Neuroprotectant delivery

When and how was the neuroprotectant therapy delivered? If an in vivo model was used, how well was the therapy tolerated by the animal? What obstacles need to be overcome in order for the neuroprotectant to be effectively delivered in humans?

MODEL SYSTEMS

Current in vitro systems differ significantly from the anatomical and cellular relationships of the in vivo aging retina and optic nerve head. Therefore, results of neuroprotection studies based on organ and tissue culture systems should be considered only preliminary information. Injury models in the intact animal, including glaucoma models, provide systems that more accurately represent the anatomic and physiological complexity of the optic nerve, retina, and optic nerve head.

Because of this, they provide a more sophisticated test of the value of potential neuroprotective agents and allow assessment of optimal dosage and delivery to the optic nerve and retina.

THE END POINTS USED TO EVALUATE THE EFFECTIVENESS OF NEUROPROTECTIVE THERAPY

Retinal Ganglion Cell Survival

Total RGC count, or more commonly RGC density, is a frequently used end point for evaluating potential neuroprotectants. Generally, RGC counts or densities following an experimental injury in a group of animals receiving neuroprotectant therapy are compared with a control group that does not receive the neuroprotectant. Several factors can complicate using this end point. First, RGCs are nonuniformly distributed throughout the retina. Therefore, sampling techniques must be random and consistent. Second, because amacrine and other nuclei may constitute a significant percentage of cells in the retinal RGC layer,^{127,128} many investigators use specific labeling to identify RGCs definitively. Usually, the label is introduced into the superior colliculus and allowed to enter the RGCs via retrograde transport. If RGCs are labeled before the injury, the label can conceivably persist following axonal degeneration, giving the impression of viability even without a functioning axon. In contrast, because retrograde labeling requires an intact axon, successfully labeled RGCs are considered viable. However, in glaucoma models with elevated IOP, the IOP may temporarily obstruct retrograde transport of the label, producing a falsely low estimate of viable RGCs.

Nerve Fiber Loss

Classically, glaucomatous injury is determined by analyzing a cross section of the optic nerve itself, using either a reduction in neural area or diminished nerve fiber count to determine the degree of damage.^{129,130} Optic nerve analysis allows one to observe the complete output of the retina in a single section and provides a direct, unequivocal measurement of the number of intact RGC fibers. Because optic nerve axons degenerate within days following their severance from the RGC soma,¹³¹ these counts also provide an accurate measure of the minimal number of surviving RGCs.

DURATION OF NEUROPROTECTION

As previously mentioned, RGC rescue by neuroprotectants can be, and frequently is, temporary. Therefore, the timing at which RGC densities or axon counts are determined is crucial for assessing the significance of studies that evaluate neuroprotection. Such studies should always determine both the extent and the duration of the observed neuroprotection.

NEUROPROTECTANT DELIVERY TO THE RETINA AND OPTIC NERVE HEAD

In many respects, the development of techniques to deliver neuroprotectant therapies to their ocular targets is just as important as discovering the neuroprotectants themselves. Because many of the proposed neuroprotectants may have widespread, significant effects on many tissue functions, specific and targeted delivery using systems tailored to the optic nerve, optic nerve head, or RGC layer of the retina will be crucial to achieving their ultimate, effective clinical use.

Many such systems are under active investigation. These include minipumps to supply neurotrophins intravitreally, and intravitreal injection and retrograde transport of adenoviral vectors, which have been successfully used to deliver genes expressing neurotrophins *in vivo*.^{75,76,132} Other potential delivery schemes include viral transfection at specific ocular sites, such as the nerve head. Because myelinated central nervous tissue is resistant to axonal outgrowth, methods to make the extracellular environment more permissive to axonal regeneration may also be useful in neuroprotection. Work along these lines includes implanting hydrogels containing either outgrowth-permissive Schwann cells into the optic nerve¹³³ or hybridoma cells that secrete antibodies to neutralize inhibitory central myelin proteins into the optic nerve.¹³⁴

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SECTION VI

LASER THERAPY OF GLAUCOMA

BASICS OF LASERS

Douglas E. Gaasterland, M.D.

Physicians treating glaucoma surgically with lasers benefit if they understand some of the properties of visible, near-visible, and invisible laser radiation in a vacuum, in air, and, especially, in tissue. This requires understanding several aspects of light:

- Radiation as a form of energy
- Laser sources of radiation
- How we evaluate energy, power, and duration
- Focusing and defocusing
- Light delivery from the laser to the target tissue
- The interaction of light with the tissue target

Laser safety is a related issue, and will be discussed at the close of this chapter.

RADIATION AND LIGHT ENERGY

Hold your hand near a glowing iron poker and you will feel the heat. This is your tangible indication of radiant transportation of energy from the metal, through the air, to your hand. Heating the iron atoms in the poker in a fire caused the outer shell electrons of the atoms to jump to a higher-energy orbit. After the poker was removed from the fire, some of these electrons started falling to their resting orbits, releasing the stored energy as electromagnetic radiation packets, called photons. Photons travel in all directions from their origin. They have both particle-like and wave-like energy properties, which account for absorption and refraction of radiation, respectively.

For all colors, the velocity of light waves in a medium is a constant characteristic of that medium. In a vacuum, it is about 3×10^8 meters/second. At all wavelengths, velocity (V) is equal to frequency (v) multiplied by the wavelength (λ).

$$V = v \times \lambda$$

Max Planck showed in 1900 that the energy in a photon is proportionate to how fast it vibrates (i.e., its frequency). Light from the shorter-wavelength ultraviolet or blue end of the spectrum has a higher frequency of vibration, and more energy per photon, than the longer-wavelength red or infrared light. This differential photon energy is especially useful in laser surgery, as we shall see in the section on target tissue effects.

LASER SOURCES

When atoms or molecules are subjected to an external source of energy, a photon discharged from one excited atom can induce the release of another photon when it passes near a second excited atom. This occurs in some, but not all, transparent media, a good example of which is an yttrium-aluminum-garnet crystal, containing some (doped with) neodymium atoms. This process of induced photon release, called stimulated emission, was first postulated by Einstein in 1917. Both photons, arising from the same type of atom, will have the same color (wavelength), will vibrate in phase (coherence), and will travel in the same direction. This amplification doubles the light energy that was present before the interaction. It can repeat again and again, provided the media contains many excited atoms (a population inversion) and the pathway through the media is long enough for the photons to encounter them.

One way to elongate this pathway is to place the excited medium between parallel mirrors. Those few photons arising from spontaneous decay and moving perpendicular to the mirrors will oscillate back and forth through the medium and quickly recruit a large number of ancillary photons.

The parallel mirrors form the boundary of a space containing the medium and numerous oscillating photons, called the laser cavity (Fig. 39-1). If one mirror is partially, instead of fully, reflective, then some of the photons escape

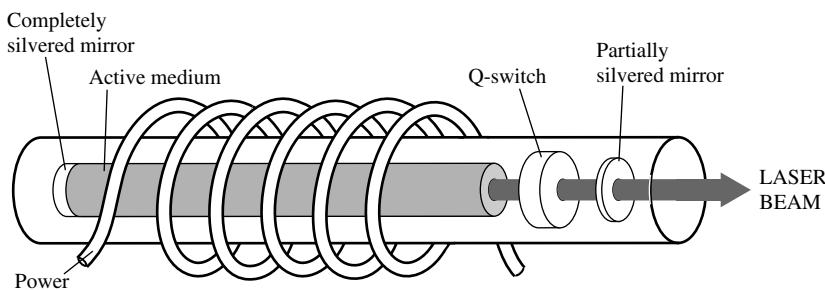


FIGURE 39-1 Schematic illustration of the basic laser cavity, power coil for input energy, and Q-switch. (Reproduced with permission from Regillo CD, Brown GC, Flynn HW, eds. *Vitreoretinal Disease: The Essentials*, New York: Thieme; 1999.)

with each oscillation and form a beam of monochromatic, unidirectional laser light. The wavelength of this output light is a characteristic of the laser medium (Table 39-1).

The name *laser* is an acronym denoting the physical principles on which this device is based: *light amplification by stimulated emission of radiation*. Lasers have three basic characteristics: (1) a source of input energy; (2) a solid, liquid, or gas medium; and (3) a cavity. For most lasers, the input energy is either light, as from a flash-lamp, or an electric spark or current. Important characteristics of laser beams are monochromicity, collimation (minimal divergence of light rays), and coherence.

Some atoms or molecules used in lasers decay from the excited, high-energy state to the ground state in more than one step. Upon decay, they emit a photon with one wavelength during the first step and another photon of a different wavelength during the second step, and so on. A laser device based on such media may put out intermixed beams of more than one color. An example of this is the argon atom, which emits several colors, the clinically important ones having blue (488 nm) and green (514 nm) wavelengths. A bandpass filter can remove all but one of the beams from its output, allowing the operator to select the green output over the blue, or vice versa. Another method to separate two intermixed beams is to pass them through a prism, taking advantage of the fact that light of one wavelength will be refracted (bent) differently from light of another wavelength.

TABLE 39-1 WAVELENGTHS OF OUTPUT LIGHT FROM VARIOUS OPHTHALMIC LASERS

Laser Medium	Wavelength (nm)	
CO ₂	10800	Far infrared
Erbium	2940	Infrared
Holmium	2100	Infrared
Nd:YAG	1064	Infrared
Diode	800–810	Infrared
Krypton	647	Red
Frequency doubled Nd:YAG	532	Green
Argon	514.5	Green
Argon	488	Blue
Excimer (ArF)	193	Ultraviolet

Nd:YAG, neodymium:yttrium-aluminum-garnet; ArF, argon fluoride.

Another important characteristic of laser instruments is whether the output is continuous [referred to as continuous wave (CW) output] or pulsed. A CW laser has continuous output while it is turned on, like a flashlight that is illuminated. Pulsed output occurs in the form of a single burst of laser light or as a series of many brief small pulses arising within a relatively brief time envelope, usually measured in milliseconds. The latter is called a free-running laser.

Q-switching is a method to delay laser output by placing a transiently opaque shutter within the cavity, allowing widespread excitation to build in the atoms within the medium. Abrupt clearing of the light blocking shutter (the switch) allows the output of a single, brief, "giant" laser pulse. Because the opaque switch "spoils" the "quality" of the cavity, this technique is termed Q-switched. The duration of Q-switched pulses is usually 5 to 20 nsec. By contrast, a pulsed output with many thousands of small pulses per second and an infinitely long time envelope may mimic the effect on tissue of a CW laser.

ENERGY, POWER, AND DURATION

Our terminology for describing laser output arises from Newtonian physics. These terms are helpful for predicting and quantitating laser-tissue interactions (Table 39-2).

TABLE 39-2 COMMON TERMINOLOGY DESCRIBING LASER OUTPUT

Term	Definition
Force	Mass multiplied by acceleration
Newton	The force required to accelerate a 1-kilogram mass at a rate of 1 meter per second each second (1 m/sec^2)
Work	The energy expended by applying a force over a distance
Joule (J)	The work of applying 1 newton of force over 1 meter
Power	The rate of work, or energy production
Watt (W)	Power at a rate of 1 joule/second (1 J/sec)
Irradiance	Radiant flux density at a surface, expressed in watts/cm ² (W/cm^2)
Radiant density	The light energy within a volume, expressed in joules/m ³ (J/m^3)

TABLE 39-3 FREQUENTLY USED PREFIXES FOR LASER PARAMETERS AND THEIR EQUIVALENT SCIENTIFIC NOTATION

Prefix	Scientific Notation Equivalent
pico-	$\times 10^{-12}$
nano-	$\times 10^{-9}$
micro-	$\times 10^{-6}$
milli-	$\times 10^{-3}$
kilo-	$\times 10^3$
mega-	$\times 10^6$
giga-	$\times 10^9$
tera-	$\times 10^{12}$

From Newton's law, force = (mass × acceleration). By definition, a newton is the force required to accelerate a mass of 1 kg at a rate of one m/sec each second (1 m/sec²). At Earth's surface, the acceleration due to gravity is about 9.8 m/sec².

Work is energy expended by applying a force over a distance. A joule is the work of 1 newton (1 N) of force through 1 m. At Earth's surface a 1 kg mass weighs 9.8 N, or 2.2 lb. Lifting a 1 kg mass for a distance of 1 m requires 9.8 joules (9.8 J) of energy. Remembering that a calorie, the energy required to heat a 1 gm mass of water by 1°C, is nearly 4.2 J, one can calculate that slowly lifting 22 lb from resting on the floor to overhead (a distance of about 2 m) requires almost 200 J, or 47 calories of work.

Power is the rate of work, or energy production. It equals work divided by the duration of time over which the work is done. A watt is power at a rate of 1 J/sec. Thus a 100 watt (100 W) light bulb has output of 1 J in 0.01 seconds, and 100 J/sec. In other words, a 1 W CW laser puts out 1 J/sec.

Irradiance is the radiant flux density at a surface and is expressed in W/cm². The radiant density is the light energy within a volume, expressed in J/m³.

When used in medicine, laser energy, power, and duration assume various measures, ranging from minuscule to massive. We use a number of prefixes, most of them familiar, to denote multiples for the magnitudes of these quantities. These prefixes are listed in Table 39-3.

FOCUSING AND DEFOCUSING

The focused spot diameter (d) for an ideal laser beam with wavelength (λ) having a uniform energy distribution in its cross section diameter (D) and traversing a uniform, thin lens of focal length (f) may be approximated by the following equation¹:

$$d = \frac{2.44}{D} \lambda f$$

An ideal laser output beam has a gaussian, rather than a uniform, energy distribution in its cross section, because the minimum spot diameter is larger when the energy distribution is not uniform.

A laser output with a shorter wavelength, an output lens with a shorter focal length, and an expanded laser beam with a larger diameter all cause a smaller-diameter focal spot. If other parameters are equal, the beam intensity is greater in a smaller focused spot, which is useful for cutting or ablating tissue.

The convergence of a laser beam coming to focus is equal to its divergence after it passes the focal point. If the beam focus is located in space in front of or behind the target, then the laser beam cross section on the target will be larger than at focus. Such defocusing allows the surgeon to adjust the treatment beam diameter on the target tissue (e.g., the retina or the trabecular meshwork) for appropriate tissue effect. Generally, it is better to defocus with the focal point behind the target plane, because it avoids a "hot spot" in the transparent media in front of the target.

LIGHT DELIVERY FROM THE LASER TO TARGET TISSUE

A surgical laser system contains, in addition to a laser, a means to deliver the laser output to the tissue target. Such delivery could be by direct contact of the output window of the laser system with the tissue. However, systems for eye surgery incorporate some intervening pathway for optical delivery. The light may travel through air to a focusing device, or there may be a fiberoptic light guide. Some commercial systems use both, with the output first traveling through a fiberoptic, then delivery optics, and then air, as it approaches the eye. Fiberoptic devices for tissue contact delivery of laser energy generally have handpieces containing terminal optics for shaping the beam.

Whatever the delivery medium, most laser beams lose photon coherence over a comparatively short distance from the laser output window. However, the beam retains monochromaticity and much of the original directionality.

Commercial laser systems provide an aiming spot, composed of either a highly attenuated portion of the treatment beam or a superimposed, coincident, low-power beam. These coincident aiming beams are usually the red output of helium:neon lasers (632 nm) or visible diode lasers.

INTERACTION OF LIGHT WITH OCULAR TISSUES

Photons traveling from a laser source through delivery optics to encounter a tissue surface may (1) reflect back toward the source, (2) bend (refract) upon passing the

surface, (3) scatter while traversing the tissue, (4) be absorbed by tissue components, or (5) traverse the tissue without interaction. Reflection from the eye surface usually involves a small proportion of the incident beam and is limited by using antireflection-coated treatment contact lenses. Refraction at the surface is affected by the angle of incidence and the difference between the index of refraction of the tissue and that of the media containing the incident beam. Quartz glass has an index of refraction about 1.45, air about 1.0, and the cornea and sclera about 1.37. Because the difference between the index of refraction between glass and tissue is relatively small ($n = 0.08$), laser delivery using contact fiberoptic devices produces less refraction than delivery through air ($n = 0.37$). Scatter occurs when the pathway of light waves traversing a tissue encounters local variations in density of the media. This causes some of the photons to bend away from the direction of travel of the beam.

Photon absorption by tissue components results in local change of molecules and atoms. When photon energy is absorbed slowly, as during treatment with CW or free-running lasers, the local effect is thermal. Photocoagulation occurs with a local temperature between 55° and 85°C, at a temperature that causes proteins to denature. The thermal effect may spread outward from the irradiated target. Local disruption occurs when the target temperature reaches 90° to 100°C, at which tissue water boils. Above 100°C, there is tissue charring, burning, and evaporation.

Photodisruption occurs when photons in the target are so tightly packed in space and time that they cause local ionization. Q-switched lasers provide this interaction, which is useful for performing iridotomies and capsulotomies. A visible spark may occur at the target site during this laser–tissue interaction. Photochemical interactions occur during the absorption of blue or ultraviolet photons, which have high enough energy to break molecular bonds. These interactions produce either ablation, as during excimer laser treatment, or cytotoxicity, when used with supplemental chromophores.

The practitioner must be mindful of healing responses that occur after laser surgery. Tissue responses are modified by preoperative medicines, inflammation, altered blood supply, aqueous humor changes, race, and postoperative antifibrotics and anti-inflammatory drugs. These can either enhance or reduce the intended effect of the laser treatment.

LASER SAFETY

Ophthalmic laser systems can cause diverse, unintended effects on the eye, cardiovascular system, and skin.² In ophthalmic systems, the beam emitted to air is either con-

verging or diverging. A collimated beam, found inside the laser console or with laser pointers, is particularly dangerous for the emmetropic eye, which can focus such a beam perfectly on the fovea.³

Electronic components housed within the laser console present another potential danger. Some of these can store electric charges that can deliver potentially lethal cardiovascular shock if contacted inadvertently. Some of these charges may remain in the capacitors even after the laser system is unplugged. The obvious advice to practitioners who have not had specific training in laser maintenance is to leave the covers of all laser systems in place.

Inadvertent exposure to certain laser wavelengths can damage skin, even if unfocused. This applies particularly to carbon dioxide, erbium, holmium, and excimer lasers. Because these beams have invisible wavelengths, the surgeon should always be aware of where the beam is located in the room, to avoid inadvertent skin exposure.

By the time an ophthalmic treatment laser output beam has traveled several meters from the delivery optics, the luminance has usually decreased, due to beam divergence, to a level unlikely to harm the eye of a casual observer. However, ocular laser surgery often uses treatment contact lenses with a flat front surface, raising the potential for a potentially harmful specular reflection.⁴ Fortunately, the surgeon is usually protected by the delivery design of the system. Nevertheless, observers should always stay out of the 2 m zone and, for additional protection, wear attenuating goggles specific to the wavelength of the system. Even better, all but required personnel should be excluded from the laser treatment suite.⁵

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LASER TRABECULOPLASTY

Alan L. Robin, M.D., and Miray Hamparian, M.D.

Argon laser trabeculoplasty (ALT) lowers intraocular pressure (IOP) either by causing focal contraction of the trabecular meshwork beams and widening of adjacent intertrabecular spaces, or by altering endothelial cell function to decrease the resistance to aqueous humor outflow. Experience over the past 20 years has demonstrated an overall initial success rate ranging from 60 to 97%. Primary open-angle glaucoma, pseudoexfoliation glaucoma, and pigmentary glaucoma typically respond best to this procedure.

The primary advantages of ALT are the extremely favorable risk:benefit ratio, offering the prospect of improved pressure control without the risks of filtration surgery. Disadvantages include the potential for postoperative pressure spikes and inflammation, both of which are usually self-limited. The major disadvantage lies in the potential for failure and the long-term loss of efficacy, approximately 10% per year. Recent work suggests that trabeculoplasty in eyes with early glaucoma may prove as effective as, if not superior to, medical therapy when used as primary glaucoma therapy. Trabeculoplasty with other lasers, including the diode and the Q-switched, frequency-doubled neodymium:yttrium-aluminum-garnet (Nd:YAG) laser present unique features that may provide additional advantages for glaucoma treatment.

BACKGROUND

The prospect of treating glaucoma with a laser that did not make an entry tract into the anterior chamber was first described by Krasnov in 1973.¹ Termed laseropuncture, this consisted of using a Q-switched ruby laser to puncture the trabecular meshwork, producing a hypotensive effect that lasted for several months.² Although similar work was later done by Robin and Pollack, the instrument was unstable, required frequent repairs, often

caused hemorrhages in the angle, and was unsuitable for wide clinical application.³

In 1974, Worthen and Wickham demonstrated that the argon laser, used to treat the angle much as we do today, could successfully lower IOP. However, the parameters of the argon laser were so varied that their results were somewhat unpredictable.^{4,5} At the same time, Gaasterland demonstrated that heavy treatment of the trabecular meshwork with the argon laser produced elevated IOP in monkeys.⁶ Because of the fear that common application of laser therapy to the anterior chamber angle could cause, rather than eliminate, glaucoma, many individuals suspended their research into laser therapy for open-angle glaucoma.

In 1979, Wise and Witter published the first pilot work demonstrating that argon laser trabecular therapy could produce consistent, relatively long-term reduction of IOP in patients with glaucoma.⁷ Their success, due in part to standardized laser protocol parameters, inspired many others to duplicate their work, and improved our understanding of the indications and success rates for this procedure.

Over the years, many different wavelengths and laser types have been used to treat the trabecular meshwork. Due to the initial ready availability of the argon laser, many individuals termed the procedure argon laser trabeculoplasty, or ALT. It was later shown that trabeculoplasty could be effectively performed with the krypton (KLT), Nd:YAG (YLT), diode (DLT), and frequency-doubled Nd:YAG (SLT) lasers. Because of this, *laser trabeculoplasty* (LTP) has also been used as a descriptive term for this procedure.

Developed at a time when partial thickness filtration surgery was in its infancy, ALT was initially viewed as an alternative to incisional surgery, and only used when maximal medical therapy was unable to control the progression of glaucoma. As experience with ALT grew, it

became an adjunct to medications as it met wider acceptance. Finally, ALT was soon considered as a first-line therapy in lieu of medications, and as its safety and efficacy were confirmed. The Glaucoma Laser Trial legitimized ALT as a potential first-line therapy.^{8,9}

MECHANISM OF ALT

Investigators have found that ALT can increase the facility of outflow by about 50%.^{10–12} There are two main theories by which this is accomplished. Although the laser energy does not penetrate the full thickness of the trabecular meshwork, it does cause a thermal burn on its surface, the loss of endothelial cells, and disruption of the trabecular beams (Fig. 40–1).

The first theory proposes that the resulting scarring and shrinkage of the treated trabecular beams puts tension on the adjacent beams, opening the intertrabecular spaces and increasing the outflow of aqueous humor.^{7,11,13} This theory is supported by pathological studies of human and nonhuman primate eyes following trabeculoplasty.^{14,15} Both show disruption of trabecular beams and cellular necrosis, with later shrinkage of meshwork collagen.

The second theory proposes that the laser in some way alters the biochemical nature of the trabecular meshwork and reduces the resistance to aqueous humor outflow.¹⁶ This is supported by pathological observations that trabeculoplasty initially reduces the number of trabecular endothelial cells in the areas of treatment, followed by increased cell division and phagocytic activity by surviving trabecular cells.^{17,18} Studies with radioactive tracers have confirmed that ALT is followed by cell division in the anterior meshwork. The cells then migrate into and repopulate the treated regions.¹⁹ Subsequent work has shown that trabecular meshwork tissues treated by ALT respond with increased production of matrix metalloproteinases, which increase the turnover of extracellular

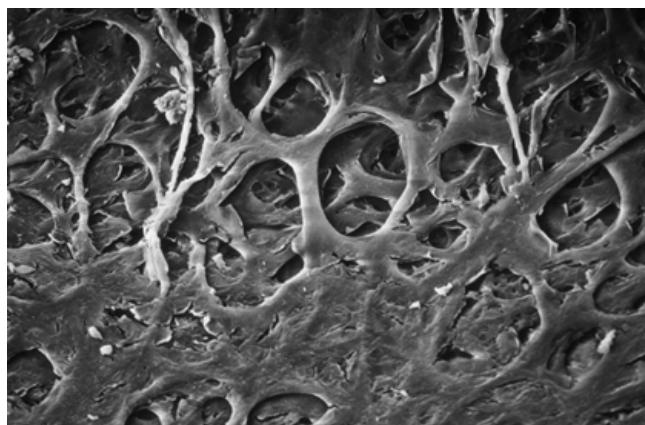


FIGURE 40–1 Scanning electron microscopy of a trabecular meshwork specimen following argon laser trabeculoplasty. Note the matted appearance of the scarred trabecular beams and loss of trabecular endothelial cells.

matrix materials.^{19a,19b} This, in turn, would be expected to diminish aqueous outflow resistance and lower IOP.

Both theories rely on a cellular and tissue response to the laser treatment. Thus they are consistent with the well-accepted observation that the final IOP lowering does not occur until 3 to 46 weeks following the procedure.

EFFICACY OF ALT

The experience of the past 25 years has helped define the efficacy of ALT in combination with medications in a wide variety of glaucomas, as well as its role as primary therapy for newly diagnosed glaucoma.

ARGON LASER TRABECULOPLASTY AFTER MAXIMAL MEDICAL THERAPY

Since the pilot study by Wise and Witter,⁷ ALT has been an important and viable option for the presurgical patient on maximal tolerated medications and uncontrolled glaucoma. However, the initial enthusiasm for ALT that resulted from the good short-term success rates^{7,11,20} was later tempered by reports of diminished success several years after the procedure.^{21,22} Some of this may result from the fact that early experience with ALT was in patients who had far advanced disease and were more likely to progress over time. In contrast, patients treated earlier in their disease could conceivably have better long-term success. In addition, many of these earlier studies used a narrow definition of success, usually an IOP less than 20 to 22 mm Hg. Thus, changes in practice patterns and technique over the years make it hard to assign accurate figures to the efficacy of ALT among the different types of glaucoma.

For all glaucomas, the initial success of ALT ranges from 60 to 97%.^{7,10,11,12,23} However, phakic patients with primary open-angle glaucoma or pseudoexfoliation generally respond better to this procedure than do those with other types of glaucoma.

Primary Open-Angle Glaucoma

In the short term, the success of ALT in primary open-angle glaucoma ranges from 80 to 97%.^{7,10,11,12,23} In addition, it is possible for some or all medications to be discontinued because the effect of ALT can be dramatic in some cases. Lieberman reported that 58% of patients could reduce their medical regimen and 5% eliminated all medications.²³

Unfortunately, the effect of ALT wanes over time. At 1 year, the success of ALT is 77 to 81%, with a subsequent yearly failure rate of 7 to 10%.^{21,24} After 5 years, the probability of success was around 57% in one study²⁴ and 35% in another,²¹ with an overall success rate of 35 to 44%. However, ALT can still be successful in up to 32% of patients after 10 years.²⁵

SPECIAL CONSIDERATION

The failure rate for ALT in primary open-angle glaucoma is approximately 10% per year.

The Advanced Glaucoma Intervention Study (AGIS) was designed to compare the effectiveness of ALT to trabeculectomy in patients with worsening glaucoma despite maximal medical therapy.²⁶ It demonstrated improved preservation of visual function, as determined by visual acuity and perimetry, in black patients, despite higher IOPs in patients with ALT as compared with trabeculectomy. White patients, on the other hand, fared marginally better when trabeculectomy instead of ALT was initially performed. Although this outcome difference between algorithms appeared to diminish with time in both racial groups, ALT was not found to be detrimental in either one.

Pseudoexfoliation

In short-term evaluations, ALT is effective in lowering IOP in pseudoexfoliation. The success rate in the first few months is 97%, with the extent of IOP lowering ranging from 12 to 17 mm Hg.^{23,27,28} In addition, medications may be discontinued in some patients postoperatively. Here, too, the effect of ALT can quickly diminish, and at 1 year the "IOP-lowering success" is in the range of 50 to 70%.^{21,23} Finally, in some cases of pseudoexfoliation, the final IOP can be much higher than baseline, leaving the patient in need of an urgent trabeculectomy.

Pigmentary Glaucoma

ALT appears to work in a number of eyes with pigmentary glaucoma. Adequate IOP lowering is reported in 44 to 80% at 1 year, followed by a gradual decline to about 45% at 6 years.^{23,29–31} Unlike patients with primary open-angle glaucoma, younger patients with pigmentary glaucoma may respond better to ALT than their older counterparts, with a longer-lasting effect. Although the role of iridotomy in pigmentary glaucoma remains controversial, the preferred laser therapy for most of these eyes remains trabeculoplasty, when indicated.

PEARL... Younger patients with pigmentary glaucoma may respond better to ALT than their older counterparts.

Aphakic and Pseudophakic Glaucoma

Aphakic eyes typically respond less well to ALT, although some individual cases may have adequate effect. Although success rates range from 60 to 85%, mean IOP lowering is only around 6 mm Hg.^{7,10,23} In addition, these patients

cannot be tapered off medical therapy after ALT, and the IOP lowering may be transient.^{7,28} If vitreous is present in the anterior chamber, ALT is almost certain to fail.⁷

Although the exact relationship between the cataract surgery and glaucoma history and the success of ALT is unknown, trabeculoplasty may have a better chance of working if the glaucoma developed prior to cataract surgery. If the glaucoma is due to complications associated with cataract surgery, ALT is far less likely to be effective. Finally, it is still unknown if intracapsular or extracapsular cataract extraction, or phacoemulsification surgery with or without clear corneal lens extraction, has an impact on laser success.

Prior Trabeculectomy

ALT can be successful in eyes with prior trabeculectomy in up to 70% of patients.^{10,28,32} The Advanced Glaucoma Intervention Study appeared to confirm this, although it still found that the IOP decrease was greatest with filtration surgery.²⁶

Angle Recession, Uveitis, Narrow-Angle Glaucoma

In general, ALT is ineffective if the trabecular meshwork is not visible, such as due to permanent peripheral anterior synechiae, a recessed angle, or iridocorneal endothelial (ICE) syndrome. Careful gonioscopy is imperative to insure that at least 180 degrees of the trabecular meshwork appears functional.

ALT is generally poorly effective in patients with uveitis. This may be due to permanent angle closure, blockage of the trabecular meshwork by particulate debris in eyes with acute uveitic glaucoma, a poor view of the anterior chamber angle, or growth of a microscopic membrane over the trabecular meshwork. In all of these cases, trabeculoplasty may potentially cause elevated IOP due to a reactivation of the uveitis and further destruction of the remaining functional meshwork.^{23,28,33}

In eyes with chronic angle closure, the exact amount of angle that must be visible and open for ALT to be effective has not been determined. Many have suggested that at least half of the angle needs to be open to treat successfully without creating a permanent IOP elevation. Here it is imperative to weigh the potential adverse effects of permanent angle damage against the chance of improving aqueous outflow. However, if the angle can be adequately visualized, some patients with angle-closure glaucoma can be successfully treated with ALT after iridotomy or iridectomy, even in the presence of peripheral anterior synechiae.^{10,28}

Eyes with angle recession generally do not respond adequately to ALT.²⁸ However, individual cases sometimes do respond well in the short term.^{10,23} In one series, 63% of eyes were considered successful after 5 months.³³ However, most of these eyes eventually required more definitive therapy.

REPEAT ALT

Repeating ALT on 180 or 360 degrees of the angle in an eye that has had a previous 360 degree treatment is usually ineffective.³⁴⁻³⁶ Successful ALT can occur in 33 to 38%, whereas about 68% will fail.³⁴ Of the eyes considered successful, the effect is short lived and the treatment effect is lost in two thirds of eyes by 1 year.^{34,36} In addition, 12 to 17% can have an acute rise in IOP of 10 to 37 mm Hg. This can result in rapid progression of visual field loss and optic nerve deterioration, and a few cases will require urgent surgery to control the IOP.^{35,37} On the other hand, early experience with selective laser trabeculoplasty (SLT), discussed in the following text, suggests that repeated treatment may provide adequate results.

ARGON LASER TRABECULOPLASTY AS PRIMARY THERAPY

ALT may also be considered as first-line therapy for the patient with newly diagnosed open-angle glaucoma.³⁸ The advantage of this approach is that it avoids the problems of noncompliance and the side effects of long-term medical therapy, as well as the negative effect of medications on the conjunctival epithelium and stroma.³⁹ Several studies have shown that, when performed as initial therapy, ALT can be very effective in reducing IOP.^{8,9,40,41} The Glaucoma Laser Trial, which compared the efficacy of initial treatment with ALT to that of initial medical therapy with beta-blockers, found that 63% of patients maintained IOP control 1 year after undergoing ALT, and 44% were controlled with ALT alone after 2 years.⁸ In addition, patients treated initially with ALT were more likely to be controlled on fewer medications. Although differences were small, an additional 3 years of follow-up revealed that eyes that received laser first had overall lower IOP and less visual field loss.⁹ In spite of these favorable results, many clinicians still tend to use medications to treat glaucoma before trying ALT.

EFFECT OF RACE, SEX, AND AGE ON ARGON LASER TRABECULOPLASTY EFFICACY

Neither race nor sex has any effect on the response or success of ALT. It is as effective in black as well as white patients.^{10,11,13,25,42} However, black patients may fare better with respect to visual field and acuity in the long term, as compared with white patients. On the other hand, patients younger than 40 years of age have a dramatic rate of failure with ALT. About 60% develop uncontrolled IOPs and require filtering surgery for control within 1 to 2 years.^{10,43} Congenital and juvenile-onset glaucomas also respond poorly to ALT.^{10,20}

PRELASER INTRAOcular PRESSURE AND ARGON LASER TRABECULOPLASTY RESPONSE

Some investigators have found that ALT produces a greater lowering of IOP in eyes with higher preoperative

pressures.^{10,40,44} However, not all studies found such a correlation,²⁵ suggesting that, overall, the percent of IOP reduction may be fairly constant.

SURGICAL TECHNIQUE FOR ARGON LASER TRABECULOPLASTY

PREOPERATIVE CONSIDERATIONS

Prior to treatment, the surgeon should insure adequate knowledge of the patient, remarkable features of the patient's angle, and the proper functioning and calibration of the laser. A pretreatment IOP measurement is essential. However, argon laser energy may be absorbed by fluorescein and can cause corneal opacities. Therefore, excess fluorescein should be irrigated from the conjunctival sac prior to treatment. Alternatively, fluorescein can be used in the untreated eye, and proparacaine in the treated eye. By app planating the eye with the fluorescein first, and then carrying this fluorescein on the tonometer tip over to the eye to be treated, epithelial exposure to the dye can be minimized.

Informed consent should include the possibility of a 1 to 3% chance of a transient IOP elevation necessitating further observation or medication, mild inflammation with injection and photophobia, or, rarely, permanent IOP elevation that may require further laser or even surgical management. Most important, the patient should understand that the procedure may not work, and that further medical or surgical therapy may be necessary.

It is advisable to treat the patient with one drop of either brimonidine or apraclonidine one half hour before and/or immediately following trabeculoplasty. These alpha adrenergic agonists have been shown effective in minimizing acute postoperative IOP elevations, as discussed in the following text.

LASER TECHNIQUE

The surgeon and the patient must both be comfortable, with the patient's head resting on the chin and forehead supports of the slit-lamp. Either a Goldmann gonioscopy lens or a Ritch trabeculoplasty four-mirror lens can be used to perform ALT, although other mirrored gonioprisms have also been used. Following instillation of a topical anesthetic, the surgeon inserts the gonioprism, using the right hand for treating the left eye and the left hand for the right eye, to allow the patient to maintain fixation with the fellow eye. An elbow rest helps keep the prism steady throughout the treatment.

Standard treatment parameters consistently include a spot size of 50 µm and 0.1 sec exposure time. The spot should be carefully focused with each application to maximize energy delivery. This is accomplished by keeping the spot size as small and round as possible. Throughout the procedure, the front plane of the prism must be kept

perpendicular to the laser delivery path. If the aiming spot is no longer round, this is most likely due to the surgeon tipping the lens in an attempt to view the angle over the iris surface. If this occurs, the surgeon should correct the lens orientation while looking around the slit-lamp at the lens position, and then have the patient shift his or her gaze, using the fixation light with the fellow eye, to improve the view of the angle, without tipping the lens. Treating through the middle third of the lens will minimize the effect of spherical aberration.

PEARL... Orienting the lens surface perpendicular to the laser beam will help keep the aiming spot well focused and round.

Laser energy levels should be titrated between 500 and 1000 mW to produce minimal depigmentation or a slight vaporization bubble in the anterior trabecular meshwork.^{7,45} Treatment spots are typically placed three degrees apart (Fig. 40–2). Because the laser energy is absorbed by pigment, the power may need to be reduced in eyes with a heavily pigmented meshwork, as is frequently seen in pigmentary glaucoma and pseudoexfoliation. Likewise, the power may need to be adjusted throughout the procedure because pigmentation can vary within a single eye. In some lightly pigmented eyes, it may be almost impossible to see the spots. Power levels above 1 W should be avoided, if possible.

Every surgeon should develop a standard routine for treating the meshwork. This minimizes the chance of getting disoriented and helps the surgeon keep track of the clock hour being treated. Many surgeons advocate begin-

ning treatment through a superior mirror, into the inferior trabecular meshwork. This is typically the deepest part of the angle, with the best view. In addition, the inferior angle is often more highly pigmented, making it easier to identify the trabecular meshwork. Applying several burns along the meshwork, and then turning the goniometer (in a direction opposite to that of the burns) to expose the next stretch of meshwork, is generally more efficient than turning the mirror slightly after each burn application. Noting angle landmarks, changes in pigmentation, and even treatment burns, when visible, helps identify the last area treated when reorienting the lens.

Anterior versus Posterior Placement of Burns

Although initial treatment protocols placed burns either on or just posterior to the most heavily pigmented portion of the meshwork,⁷ this method was associated with pain, acute rises in postoperative pressure, and the formation of posterior synechiae. Anterior treatment, so that each spot straddles the junction of the pigmented and nonpigmented trabecular meshwork, appears to diminish all of these problems when compared with treatment of the posterior meshwork.⁴⁵ However, the surgeon should beware of confusing pigment that occasionally appears anterior to Schwalbe's line with the pigmented trabecular meshwork because this can cause inadvertent treatment to the peripheral cornea. Often, pigmentation might disappear as one moves from the inferior to the superior meshwork. This can be remedied by "back-tracking" to the last area treated.

180- versus 360-Degree Treatment

The original protocols for ALT involved placing 100 spots around the entire 360 degree circumference of the angle. Subsequent studies suggested that 180-degree treatments were less likely to produce marked postoperative IOP elevation.^{45,46} This has led many surgeons to perform ALT in 180-degree increments, assessing the effects of the first treatment after 1 month. If the desired level of IOP has not been achieved, the other half is treated because some patients respond when the entire angle is treated, even when some response was initially attained. If, however, significant IOP reduction does occur, the rest of the angle is not treated and saved for treatment at a later date, if necessary.⁴⁴

However, as will be discussed, the routine use of apraclonidine and brimonidine with ALT has diminished the incidence of acute postoperative IOP elevations to less than 5%, even following 360-degree treatment. Although there appears to be no striking difference in IOP lowering between the two approaches, eyes that respond well to ALT seem to have a larger absolute reduction when the entire angle is treated.⁴⁷ In addition, better long-term success with ALT has been correlated with applying 100 or more burns to the entire angle, although excessive treatment can result in a postoperative pressure increase.⁴⁸

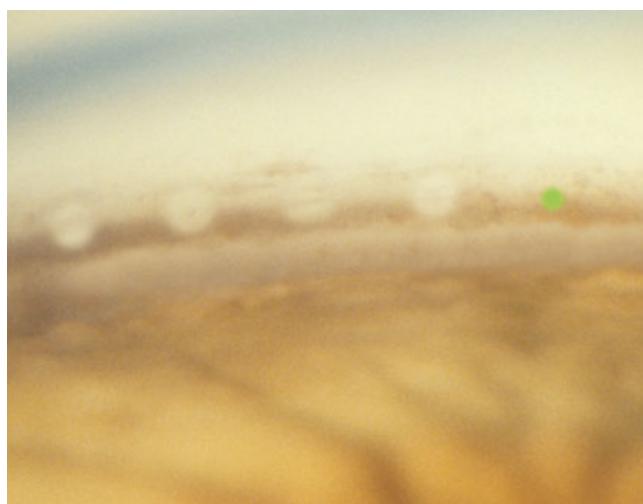


FIGURE 40-2 Representation of anterior chamber angle appearance during argon laser trabeculoplasty, illustrating slight blanching of the freshly treated trabecular meshwork regions, spaced approximately 3 degrees apart. Proper placement of the aiming beam, at the junction of the pigmented and nonpigmented meshwork, appears at right.

CONTROVERSY

Many surgeons perform argon laser trabeculoplasty in 180-degree increments, whereas others prefer to treat the entire angle at one sitting.

From these considerations, many surgeons prefer to treat the entire angle at one sitting and save the patient the expense and inconvenience of two treatments. Currently, no prospective, well-controlled studies have validated the superiority of either approach, and the question of 180- versus 360-degree treatment comes down to regional preferences.

POSTOPERATIVE MANAGEMENT

The IOP should be measured approximately 30 to 60 minutes following treatment. If the pressure is not elevated or only minimally elevated, the patient can be discharged. If the pressure is elevated, the patient should be monitored or treated, if necessary, with medications until the IOP is back to baseline or clearly returning to a safe level.

Glaucoma medications should not be discontinued immediately after ALT, but continued for at least 4 to 6 weeks, to allow sufficient time for a response. At this time, a decision can be reached whether any medications can be discontinued, but in most cases medications will still be required to achieve an IOP that is lower than the pretreatment pressure.¹²

Most clinicians prescribe topical corticosteroids, usually 1% prednisolone, four times a day for 1 week to control postoperative inflammation.^{10,11,23,49} However, no articles have confirmed a definite cost-effective benefit from this treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also be effective in curtailing inflammation,^{50,51} although other studies found that topical flurbiprofen was no different than placebo in terms of clinically assessed inflammation and comfort.^{52,53}

COMPLICATIONS OF ARGON LASER TRABECULOPLASTY

INCREASED INTRAOCULAR PRESSURE

The most important and potentially dangerous complication of ALT is an acute, usually self-limited, rise in IOP as early as 1 hour, or sooner, after treatment. Without prophylaxis, about one third of patients can have rises in IOP over 5 mm Hg, and 12 to 50% will have rises over 10 mm Hg 1 hour after treatment, with one documented IOP rise of up to 33 mm Hg.⁵⁴ As already discussed, the incidence in the rise of IOP is similar after treating either 180 or 360 degrees.⁵⁵⁻⁵⁷ This acute rise in IOP does not

indicate long-term failure of the procedure.⁵⁵ However, it can cause loss of central fixation in advanced cases of glaucoma^{10,56} as well as progression of visual-field loss.⁵⁶

Both brimonidine and apraclonidine effectively prevent a rise in IOP in all but about 3 to 5% of cases.^{58,59} Both medications are effective instilled 1 hour before and immediately following treatment, or using it only after the laser treatment.^{60,61}

PERIPHERAL ANTERIOR SYNECHIAE

Small, peaked, "tentlike" peripheral anterior synechiae (PAS) can occur in up to 46% of patients by 3 months after treatment.^{54,57,62} This rate may be higher in eyes with brown irides, or in cases where the laser burns are applied to the posterior meshwork or ciliary body band.^{54,62,63} These PAS are usually to the posterior trabecular meshwork and do not correlate with IOP rise or average laser power.⁵⁴

INFLAMMATION

Inflammation after ALT treatment can occur in up to 49% of cases and generally peaks 2 days after treatment. Up to 100% of eyes with pigment dispersion and 69% of eyes with pseudoexfoliation will have inflammation, compared to 23% with POAG.⁵⁰ Inflammation is not associated with pressure increases⁵⁴ and, to the contrary, appears to correlate with pressure decrease in the short term⁵⁰ and can be treated with either corticosteroids or NSAIDs.^{50,57} Most of the time it is clinically insignificant, and patients are asymptomatic, even when treated with a placebo.

Rarely, inflammatory precipitates can form on the trabecular meshwork, which are thought to be secondary to trabeculitis following ALT. This usually occurs a few weeks after the treatment and is associated with elevated IOPs.⁶⁴

PROGRESSIVE FIELD AND VISION LOSS

Visual field and central vision loss from a significant rise in IOP can develop very rapidly following ALT treatment.^{10,56,65} As a result, some patients may require emergency glaucoma surgery for marked and sustained pressure elevation.⁶⁵ Field loss and progression can also occur despite a decrease in IOP as a result of ALT. This is usually due to inadequate IOP lowering and progression of the disease itself.⁵⁷

TRABECULOPLASTY WITH OTHER LASERS

Although argon blue or green irradiation (488 through 515 nm) have been widely accepted for performing trabeculoplasty, other lasers can produce a comparable decrease in IOP. These include the krypton red (647 nm),⁶⁶ continuous wave (CW) Nd:YAG (1064 nm),⁶⁷ diode (810 nm),⁶⁸ and frequency-doubled Nd:YAG (fd-YAG) (532 nm).⁶⁹ Early experience with the latter two shows potential unique advantages for glaucoma treatment.

DIODE LASER TRABECULOPLASTY

The semiconductor diode laser has been shown to produce a decrease in IOP comparable to ALT.^{68,70} However, this solid-state laser has the great advantage of being durable, compact and portable, adaptable to the standard biomicroscope, and less expensive, and it uses standard electric current. The same laser can be used for transscleral cyclophotocoagulation (Chapter 42) and photoocoagulation of the retina.

For diode laser trabeculoplasty (DLT) the patient sits at the biomicroscope to which the laser has been adapted, and the procedure is similar to that used with ALT. Using a 75 μm spot size, 750 to 1000 mW of power is delivered with 0.1 to 0.2 sec duration to either 180 or 360 degrees of the trabecular circumference. Compared with ALT, DLT produced less visible reaction in the anterior chamber angle, less postoperative flare, less postoperative pain, and fewer PAS.⁷¹ In a study of 25 eyes followed for 24 months, the ocular hypotensive effect of DLT was equivalent to ALT.⁷²

The mechanism by which DLT lowers the IOP is presumed to be the same as with ALT. A comparison of the trabecular pathology after DLT and ALT revealed similar alterations in the trabecular meshwork.^{73,74}

SELECTIVE LASER TRABECULOPLASTY

Selective laser trabeculoplasty (SLT) describes trabeculoplasty using a Q-switched, frequency-doubled Nd:YAG laser.⁷⁵ In a nonrandomized, prospective 26-week study, trabeculoplasty with this laser significantly reduced the IOP both in open-angle glaucoma eyes undergoing their first laser treatment and in eyes that had had previous ALT.⁷⁶ In a prospective trial 36 patients were randomized to treatment with either SLT or ALT and followed for 6 months. SLT was equivalent to ALT in lowering IOP during the first 6 months after treatment. Equally important, patients with previous failed ALT had a significantly greater drop in IOP when treated with SLT compared with retreatment with ALT.⁷⁷

Patients are treated at the biomicroscope with the fd-YAG laser (Selecta 7000, Coherent, Inc., Palo Alto, CA) emitting at 532 nm with a pulse duration of 3 nsec and a spot size of 400 μm . The helium-neon aiming beam is focused onto the pigmented trabecular meshwork and 180 degrees of meshwork is treated with approximately 50 adjacent spots. Pulses of 0.8 mJ energy are adjusted in 0.1 mJ decreasing increments until there is no cavitation bubble formation.⁷⁷

The mechanism by which SLT lowers IOP may be similar to that of ALT. Like ALT, SLT increases the number of monocytes and macrophages present in the treated trabecular meshwork tissues and may cause release of factors and chemoattractants that are required to recruit macrophages. These macrophages, in turn, clear the pigment granules from the trabecular meshwork.⁷⁸ However, unlike ALT, SLT does not produce mass destruction of

cells and trabecular beams or result in scar tissue.⁷⁹ This is believed to result from selective photothermolysis of trabecular melanin granules, whose absorption spectrum includes the wavelength of the fd-YAG laser. The short, 3 nsec pulse confines the heat to the target tissue without spreading outside the irradiation zone. Because there is no widespread tissue destruction, it has been suggested that SLT might be effectively repeated.^{76,77}

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LASER IRIDOTOMY

Alan L. Robin, M.D., and Babak Eliassi-Rad, M.D.

Laser iridotomy is now the preferred method for managing a variety of angle-closure glaucomas that have at least some component of pupillary block. Although laser iridotomy was first described with the argon laser, iridotomy with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has now become the preferred procedure of most surgeons. This is due to the ready availability of these lasers for posterior capsulotomy and a simpler, more rapid iridotomy protocol with less chance of subsequent iridotomy closure. Complications include iris bleeding with the Nd:YAG laser, iridotomy closure with the argon laser, and pressure spikes and inflammation with both. The impact of the latter are significantly reduced by medical treatment with alpha₂-agonists and postoperative corticosteroids.

BACKGROUND

Angle-closure glaucoma caused by relative or absolute pupillary block is treatable by creating a full-thickness opening in the iris, therefore bypassing the pupil. Prior to the advent of lasers, this was achieved with a surgical iridectomy. Although successful, this procedure was associated with many complications, such as hemorrhage, infection, wound leak, flat anterior chamber, cataract, and problems related to anesthesia.¹ Frequently, patients falsely associated poor visual results with the surgery and not with their delay in seeking therapy, nor with cataract, corneal decompensation, or long-term glaucoma damage. Many patients with acute angle-closure glaucoma in one eye and an occludable angle in the fellow eye were therefore often reluctant to seek treatment for their fellow asymptomatic eye, leaving them vulnerable to angle-closure attacks or chronic angle closure.

In 1956, Meyer-Schwickerath² reported the use of light energy with a xenon arc photocoagulator to create a patent iridotomy. Not a true laser, the xenon arc was asso-

ciated with corneal and lenticular damage because of the large amounts of total, noncollimated energy required.²

In the early 1970s the argon laser attached to a slit-lamp delivery system became commercially available.^{3,4} By the mid to late 1970s, L'Esperance,⁵ Abraham,⁶ and Pollack⁷ all reported successful iridotomy formation using this laser. Because the argon laser was easy to use, convenient for the ophthalmologist and the patient, and associated with fewer complications than surgical iridectomy, it replaced iridectomy as the initial procedure of choice for various angle-closure glaucomas by the early 1980s.⁸ During this time, ophthalmologists began evaluating the advantages of the Nd:YAG lasers over the argon. The Nd:YAG laser required fewer pulses and less total energy and had a diminished rate of iridotomy closure. Today it is the laser of choice for iridotomy.

MECHANISM

Histological evaluation of the iris following a successful iridotomy demonstrates a through and through hole. Posterior synechiae are often evident surrounding the border of the hole. The argon laser primarily acts by producing a thermal burn and depends on energy uptake by pigmented tissues. Following argon laser iridotomy, there is coagulative necrosis of the adjacent stroma, migration of pigment-laden macrophages into the stroma, and loss of pigment epithelium. In time, iris atrophy may develop around the hole (Fig. 41-1A).

By contrast, the Nd:YAG laser creates a plasma of free ions and electrons at the site of optical breakdown (Chapter 39). This photodisruption releases shock waves that mechanically rupture the tissue without depending on uptake of laser energy by tissue pigment. Histology demonstrates disruption of the iris pigment epithelium surrounding the iridotomy site. In contrast to the argon

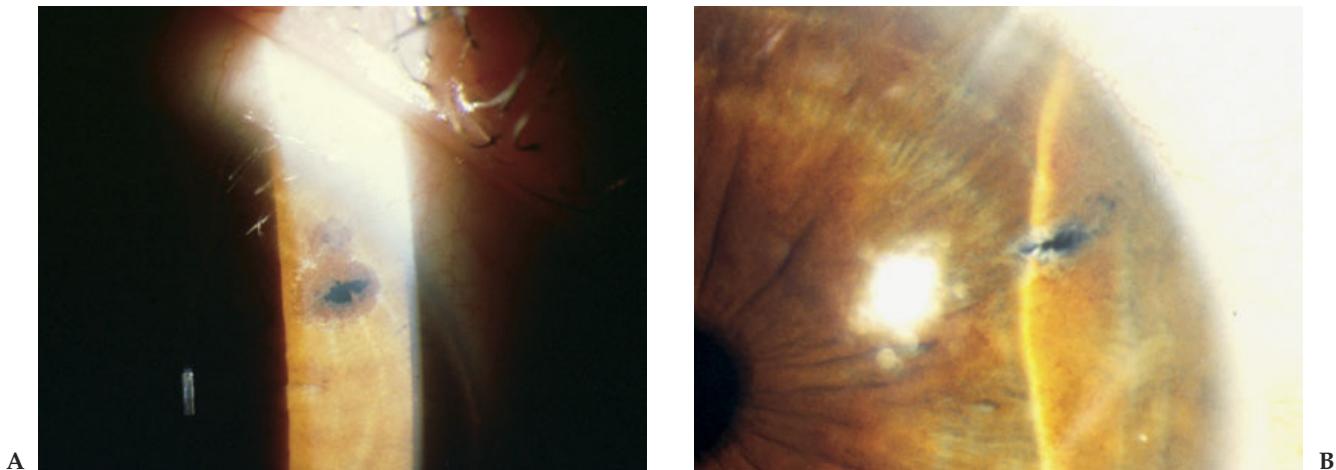


FIGURE 41-1 (A) Argon laser iridotomy typically produces coagulative necrosis, with migration of pigment-laden macrophages. The resulting opening usually demonstrates a cuff of pigment and occasionally stromal atrophy. (B) In contrast, a Nd:YAG iridotomy usually demonstrates disrupted iris stroma, without surrounding pigment proliferation.

laser, there is no coagulative effect in the adjacent stroma, and cell migration is also less likely (Fig. 41-1B).

INDICATIONS FOR LASER IRIDOTOMY

Laser iridotomy is the procedure of choice in all forms of angle-closure glaucoma (Chapter 16) in which there is a component of pupillary block.⁸ It is also helpful in distinguishing pupillary block from both plateau iris syndrome and ciliary block glaucoma. An example of the latter might be an eye with a flat chamber and elevated intraocular pressure (IOP) 1 day after cataract surgery. It is not indicated in cases of secondary angle closure where pupillary block is not a contributing factor.

ACUTE ANGLE-CLOSURE GLAUCOMA

It is easiest to create a full thickness iridotomy in an eye with clear media and with the iris as thin as possible. Because of this, laser iridotomy is best performed 24 to 48 hours after the acute attack is controlled with medical therapy, when the media is clear and inflammation is resolving. In some cases, medical therapy fails to break the acute attack. Here, some surgeons prefer to use the argon laser first, to minimize iris bleeding in these inflamed eyes with engorged blood vessels.⁹ However, medications that cause iris vasoconstriction, such as apraclonidine or brimonidine, can minimize this complication.

CHRONIC ANGLE-CLOSURE GLAUCOMA

Eyes with chronic angle-closure glaucoma are at risk of developing progressive trabecular meshwork damage and elevated IOP, as well as an attack of acute angle-closure glaucoma.⁸ In such eyes, eliminating pupillary block by laser iridotomy can minimize these potential complications.^{10,11} In addition, by allowing the angle to open to its full potential, iridotomy permits the clinician to evaluate

the state of the angle by gonioscopy and determine if further medical or surgical therapy is indicated.

APHAKIC OR PSEUDOPHAKIC PUPILLARY BLOCK

Laser iridotomy has been successfully used to relieve aphakic and pseudophakic pupillary block.^{12–15} Persistence of angle closure despite a patent iridotomy may indicate the presence of malignant (aqueous misdirection or ciliary block) glaucoma, which requires disruption of the anterior hyaloid face or vitrectomy.^{16,17}

MALIGNANT GLAUCOMA (AQUEOUS MISDIRECTION, CILIARY BLOCK)

When this condition is present, bilateral prophylactic laser iridotomies may protect the fellow eye against both acute angle-closure glaucoma and malignant glaucoma that could be triggered by subsequent intraocular surgery.⁸

PROPHYLACTIC LASER IRIDOTOMY

Prophylactic laser iridotomy is indicated in the fellow eye of patients with either acute or chronic angle-closure glaucoma, particularly if the eye has a relatively narrow angle and is thought to be capable of occlusion.⁸ Eyes with spontaneous appositional closure on darkroom gonioscopy and eyes with narrow angles and positive provocative tests should also have a prophylactic iridotomy (Chapter 16).

NANOPHTHALMOS

Eyes with nanophthalmos are characterized by a short axial length and are associated with narrow, crowded anterior chamber angles. Because of these anatomic features, these eyes are at considerable risk for developing angle-closure glaucoma and often require prophylactic laser iridotomies. However, bilateral nonrhegmatogenous

retinal detachments have been reported following laser iridotomy in eyes with nanophthalmos.¹⁸

PIGMENT DISPERSION SYNDROME

In recent years, reverse pupillary block, where aqueous humor becomes paradoxically trapped in the anterior chamber and causes posterior bowing of the iris, has been recognized as a factor in pigment dispersion syndrome (Chapter 19). Laser iridotomy bypasses this relative pupillary block and may eliminate the pressure differential across the iris.^{19,8} By eliminating the resulting iris concavity, an iridotomy can limit pigment release and the wide fluctuations in IOP seen in some patients with this condition, particularly those with marked iris concavity and very deep anterior chambers. However, many eyes with this condition simply become easier to control with time, whereas others respond well to medical management, and others to argon laser trabeculoplasty. Thus, the role of laser iridotomy for eyes with pigment dispersion and pigmentary glaucoma is not well established.

CONTRAINDICATIONS

Relative contraindications to laser iridotomy include poor visualization of the iris because of moderate corneal edema or corneal opacification, flat anterior chamber, and angle closure caused by peripheral anterior synechiae (PAS) [i.e., uveitis, neovascular glaucoma, or the irido-corneal endothelial (ICE) syndrome].⁸ Additional contraindications are children and patients who cannot keep their head still, cannot sit comfortably at the laser, or are otherwise unable to comply with the treatment protocol. In some cases, peribulbar anesthesia will permit successful treatment. Some lasers are designed to allow treatment of the patient in the supine position, and will permit treatment under general anesthesia.

SURGICAL TECHNIQUE

PREOPERATIVE CONSIDERATIONS

Informed consent for either argon or Nd:YAG therapy should include a discussion of several potential complications. These include the possibility of incomplete iridotomy and the need for a subsequent treatment session, late closure of the iridotomy, IOP elevation during the immediate postoperative period, iris bleeding (Nd:YAG), and continued IOP elevation requiring medical or surgical intervention. Patients should also be warned of a loud noise or thumping sound in the eye (Nd:YAG) and post-operative inflammation with possible headache, photophobia, hyperemia, and blurred vision.

MEDICAL THERAPY

All patients should be pretreated with topical 1 or 2% pilocarpine approximately 30 to 60 minutes prior to the

iridotomy. This stretches the peripheral iris, thus making it thinner and easier to penetrate. In addition, its miotic effect helps fixate the iris and minimizes the tendency of the pupil to peak toward the iridotomy site, a problem that is more common with the argon laser.¹ Higher concentrations of pilocarpine should be avoided because they may narrow the angle, making it more difficult to create an iridotomy without causing a corneal opacity.

One drop of apraclonidine HCl 0.5 or 1.0% or brimonidine tartrate 0.15% or 0.2%, administered at least 30 minutes prior to laser therapy, decreases the incidence of large postoperative rises in IOP from 30% to less than 5% for both argon and Nd:YAG laser iridotomy.^{20–22} As a further advantage in eyes undergoing Nd:YAG laser iridotomy, the vasoconstrictive alpha₁ action of apraclonidine (brimonidine has minimal alpha₁ effect) minimizes bleeding, improving the safety and ease of completing the iridotomy.

CONTACT LENS

A contact lens, following topical anesthesia with propracaine HCl 0.5%, offers several advantages for performing a laser iridotomy.²³ The lens concentrates the laser energy at the level of the iris, increasing the power density at the iris surface and decreasing it at the cornea and the lens. It also acts as a heat sink, minimizing the number of corneal epithelial burns. In addition, the lens magnifies the target site with less loss of depth of field than would occur if magnification is simply increased with the slit-lamp controls. Finally, a contact lens acts as a speculum; it helps separate the lids and minimizes fine eye movements.

Although several different contact lenses have been developed for laser iridotomy, the Abraham lens and the Wise lens are the most commonly used. The Abraham lens²⁴ is a modified Goldmann-type fundus lens with a flat glass plate bonded to its anterior surface. The glass plate has a +66.0 diopter planoconvex button bonded into a decentered 8 mm hole (Fig. 41–2). Antireflective

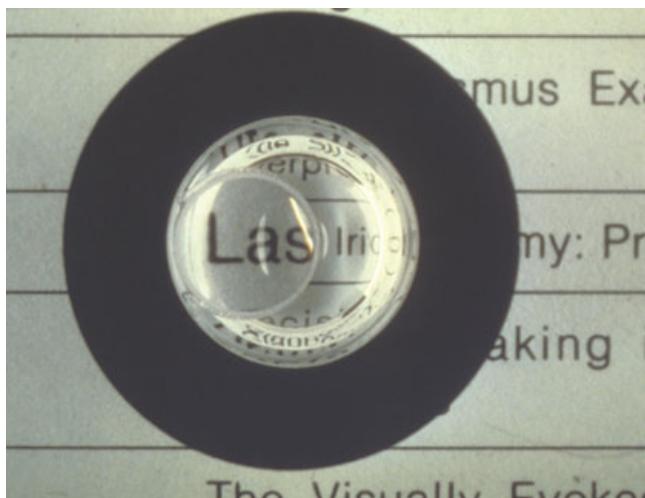


FIGURE 41–2 Abraham laser iridotomy lens.

coating on the front surface of the lens improves energy transmission and slightly increases brightness and contrast. When the laser beam is directed through the Abraham lens its diameter is doubled at the cornea and halved at the iris, which increases the concentration of energy at the iris and decreases it at the cornea. Posterior to the site of focus, the beam is more rapidly defocused, decreasing potential injury to the posterior segment.^{25,26}

The Wise lens has a +102.0 diopter button, permitting higher energy density.²⁷ This lens is more difficult to use than the Abraham lens because it provides a high amount of magnification and limited depth of focus.

When using either lens, it should be held between the thumb and first finger, allowing the fourth and fifth fingers to rest on the patient's cheek or temple to improve stabilization. Holding the lens with the left hand for the right eye, and the right hand for the left eye will allow the patient to fixate with the fellow eye. The plane of the lens must always be oriented parallel to the iris plane and the laser spot centered within the button.

SELECTION OF IRIDOTOMY SITE

Ideally, an iridotomy should be placed beneath the upper eyelid to minimize the chances of postoperative glare or diplopia, and located slightly temporal to minimize the risk of accidental macular damage. Avoiding the 12 o'clock position will decrease the chance of the iridotomy site becoming obscured with gas bubbles during the procedure, especially with the argon laser. Most surgeons choose an iris crypt, or other naturally thin area, to facilitate iris penetration. Avoiding obvious iris blood vessels, particularly with the Nd:YAG laser, will minimize the chance of bleeding.

The iridotomy should be made in the mid or far peripheral iris, just anterior to any arcus senilis. At this position, the anterior convexity of the crystalline lens has begun to curve away from the iris. This usually represents a compromise between keeping the iridotomy away from the lens capsule, but not too close to the corneal endothelium. In addition, this location maximizes the chances of visualizing the iridotomy after surgery and minimizes the chances of postoperative diplopia.

SPECIAL CONSIDERATION

The laser iridotomy should be positioned in the mid to far peripheral iris. This minimizes the risk of damage to the lens capsule and the corneal endothelium.

LASER FOCUS

Adjusting the aiming beam to a crisp, round (not oval) spot on the iris insures a precise laser focus. Because the iris is thick, the surgeon must continually adjust the focus,

especially when drilling through an iris with the argon laser. With both the YAG and the argon laser, the laser beam must be centered within the convex button with the contact lens held parallel to the surface of the iris.

If a corneal opacity does develop and inhibits the view of the iris, the surgeon can still proceed by asking the patient to look up, or in another direction. This allows the laser energy to travel through a different area of the cornea toward the iris and bypass the clouded area. When using the argon laser, keeping the patient's gaze nonparallel to the laser path will also minimize the chance of inadvertent macular damage.

ARGON LASER IRIDOTOMY

Three basic techniques have been described for creating an argon laser iridotomy: the direct technique, the "hump" method,²⁸ and the "drumhead" technique.^{29,30} For all of these methods, the basic approach is first to direct the laser beam at the iris stroma and then at the iris pigment epithelium.³¹ These techniques are not ideal for all situations, and the argon laser iridotomy technique may have to be adjusted, depending on the iris color.

Many surgeons generally use the direct technique to perform an argon laser iridotomy. This consists of simply directing repeated laser energy pulses at the same iris location until the anterior lens capsule is visible. Transillumination defects alone do not guarantee a patent iridotomy. Remember that similar defects are commonly seen in pigmentary dispersion syndrome, even though the iris stroma is intact.

PITFALL... Transillumination defects alone do not guarantee a patent laser iridotomy. Treatment should be continued until the anterior lens capsule is visible.

This technique uses 50 μm spots for 0.2 sec duration to maximize the energy density at the site of treatment. The smaller the spot size, the greater the energy or power density. A power setting of 1 W is usually ideal for most eyes. This maximizes the iris burn, with minimal surrounding char, and with minimal damage to the cornea and lens on either side of the iris.

Occasionally, an air bubble develops and blocks the view of the iridotomy site. This can often be dislodged by aiming a 50 μm spot with 300 to 500 mW power at the inferior margin of the bubble. However, aiming at the center of the bubble may also reflect the laser energy back toward the cornea and cause a corneal burn.

For medium-brown irides, some surgeons will initially create a crater in the iris stroma, and then penetrate the iris pigment epithelium through the crater's center. The approximately 500 μm diameter crater is made using several laser applications with spot size 500 μm , power 700 to 1000 mW

(average 1000 mW) and duration 0.2 sec.³¹ Further laser applications are directed at the bed of the crater until a cloud of pigment develops. This suggests that the iris stroma has been eliminated and only iris pigment epithelium remains.

At this stage, the laser settings can be changed to a spot size/power ratio of 100 μm /500 to 700 mW, or 50 μm /200 to 600 mW. Higher energy levels can dislodge adjacent iris pigment epithelium (cascade phenomenon), resulting in closure of the iridotomy.³¹ The same laser settings are used to remove the iris pigment epithelium layer regardless of iris color. This two-staged technique for the medium brown iris takes 30 to 60 laser applications. The laser procedure is considered completed when the anterior lens capsule is seen through the iridotomy site.³²

Patients with a dark brown iris may be more difficult to penetrate, due to a thicker iris stoma and fewer crypts. Thick brown irides also tend to char more easily. This char has an aluminum-like appearance and characteristic that reflects further laser energy, making it more difficult to penetrate. To prevent this problem, some surgeons advocate a “chipping” technique.^{28,33,34} Here, the duration is decreased to 0.02 to 0.05 sec and the spot size and power remain the same (using a 50 μm spot size and 700 to 1000 mW power level). This technique often requires many more laser applications (200 to 300) to penetrate the stroma³¹ and can be much more tiring for both the patient and the physician. Once the stromal crater has been eliminated, the iris pigment epithelium can be removed by the previously described method.

PITFALL... Penetrating a light blue iris with the argon laser is more difficult because of poor energy absorption by the relatively depigmented iris stroma.

Conversely, a light blue iris may be more difficult to penetrate because there is less stromal absorption of the laser energy due to the decreased pigment.^{31,32} Stetz et al. have recommend a two-step technique for eyes that lack any area of increased pigmentation.³⁵ First, long (0.2 to 0.5 sec) overlapping burns with a large spot size (500 μm) and 200 to 300 mW power are used to create a localized, tan-colored area of increased stromal density. Next, the laser settings are changed to spot size 50 μm , power 500 to 700 mW and duration 0.1 sec to create a full-thickness hole in the stroma, as already described. Alternatively, Kolker³⁴ and Hoskins and Migliazzo³⁶ use two to three applications with spot size of 50 μm , power 1000 to 1500 mW and duration 0.5 sec to create a hole in the stroma. In either case, the iris pigment epithelium layer is then eliminated using the previously described technique.

NEODYMIUM:YAG LASER IRIDOTOMY

Over the last decade, the Nd:YAG laser has become the preferred method of creating an iridotomy. This is due to

the increased popularity of extracapsular cataract surgery with posterior chamber intraocular lenses, and the concomitant increased availability of Nd:YAG lasers for posterior capsulotomies. In addition, the Nd:YAG laser iridotomy is both easier and safer for the patient and the physician. The iridotomy rarely closes following Nd:YAG laser iridotomy, and it usually can be completed with at least one tenth the number of laser pulses required for an argon iridotomy.

In general, a higher energy setting with the Nd:YAG laser increases the likelihood of penetrating the iris in one treatment setting. However, increasing the energy also increases the chance of iris bleeding. Treatment typically begins with approximately 7 to 10 millijoules (mJ) of energy.^{8,31} If well focused, 7 to 10 mJ might penetrate 75% of the time with the first pulse. In thick brown irides, or otherwise difficult eyes, increasing the energy to 10 mJ or the burst mode to two shots per pulse may help.

The main disadvantage of the Nd:YAG laser is that it has minimal thermal effects and does not cauterize the tissue as it penetrates. Instead, it disrupts the tissue, and this can cause bleeding from vessels that lie deep within the stroma.

Typically, the surgeon can control bleeding at the slit-lamp by pressing on the contact lens. This temporarily increases the IOP and collapses the iris blood vessels. After approximately 30 seconds, the pressure is released while watching the iridotomy site. If bleeding begins again, the pressure is resumed. If not, the surgeon can decide whether to continue the procedure, avoiding obvious blood vessels, or quit if the iridotomy is adequate. In general, if an initial treatment session is unsuccessful, the iridotomy can be easily completed 1 to 3 weeks later. If an argon laser is available, the bleeding vessel can be promptly and easily cauterized using 50 to 100 μm spots for 0.2 sec.

POSTOPERATIVE MANAGEMENT

The IOP should be determined 30 to 60 minutes after the procedure. If there is any increase from baseline, the IOP should be rechecked after another 30 minutes to rule out any further increase that may need medical treatment. If there is a postoperative IOP spike of 8 mm Hg or more, or if the patient has extensive disk cupping, it is advisable to reevaluate the patient in 1 day. Significant rises in IOP are treated with standard medical glaucoma therapy. Most surgeons routinely treat patients with topical corticosteroids for several days (Table 41-1) and perform a follow up evaluation 1 week after the procedure.

Once a patent iridotomy is confirmed, the eye should be dilated, to minimize posterior synechiae and examine the fundus. This is especially important following argon laser iridotomy. If posterior synechiae do exist, pharmacological stretching of the synechiae may cause bleeding at the iris-lens border. Although this bleeding is self-limited, the patient should be warned about the possibility of a temporary decrease in vision.

TABLE 4I-1 PERIOPERATIVE MEDICATIONS FOR LASER IRIDOTOMY

Medication	Concentration	When	Why
Pilocarpine	1 or 2%	1 hour to 30 minutes prior to therapy	Put iris on stretch Minimize IOP rise
Apraclonidine or Brimonidine tartrate	0.5 or 1% 0.2%*	1 hour to 30 minutes prior to therapy (can also be used immediately postoperatively)	Minimize IOP rise Reduce iris bleeding (Nd:YAG) Minimize IOP rise
Topical corticosteroids		Starting after iridotomy for 4 days to 1 week, q.i.d.	Reduce inflammation and decrease the risk of iridotomy closure (argon)

*Now only available as 0.15% concentration.

IOP, intraocular pressure; Nd:YAG, neodymium:yttrium-aluminum-garnet.

COMPLICATIONS

Complications of laser iridotomy include iris bleeding, focal cataracts, increased IOP, inflammation, and late closure of the iridotomy. Iris hemorrhage is restricted to Nd:YAG iridotomies. Iris bleeding can obscure the iridotomy site, interfere with successful completion of the iridotomy, and encourage postoperative closure of a patent iridotomy. In addition, bleeding can produce a layered hyphema and cause transient elevation of IOP (Fig. 4I-3). Lens opacities generally occur if the iridotomy site is located too close to the pupil, where the iris is still in contact with the lens capsule. They can result from heat buildup during argon laser iridotomy, or from direct tissue disruption by the Nd:YAG laser (Fig. 4I-4).

A transient, large postoperative IOP elevation can occur in approximately 30% of eyes undergoing iridotomy, regardless of the type of laser used.^{20–22} As stated above, routine treatment with apraclonidine or brimonidine significantly reduces the risk of this complication.

Nearly all eyes develop inflammation following laser iridotomy. If topical corticosteroids are not used, this can produce moderate discomfort. There appears to be no need for systemic corticosteroids, nor is there any proven benefit of topical nonsteroidal anti-inflammatory agents. Four to 7 days of topical therapy is sufficient for most cases.

Posterior synechiae can often develop after the iridotomy. In some, this may be severe enough to limit the pupil size, making subsequent perimetry, ophthalmoscopy, and cataract surgery more difficult. Avoiding postoperative pilocarpine, using frequent topical corticosteroids, and dilating the eye as soon as possible after the treatment can all minimize this complication.

Closure of the iridotomy appears limited, on the whole, to argon laser iridotomies and occurs in approximately 30% of cases. Most occur within the first month after therapy. Beyond this time, iridotomies will rarely close if there is no underlying inflammation. If closure does occur, another burst of laser energy will generally easily reopen the iridotomy.



FIGURE 4I-3 Iris bleeding and hyphema following Nd:YAG laser iridotomy.

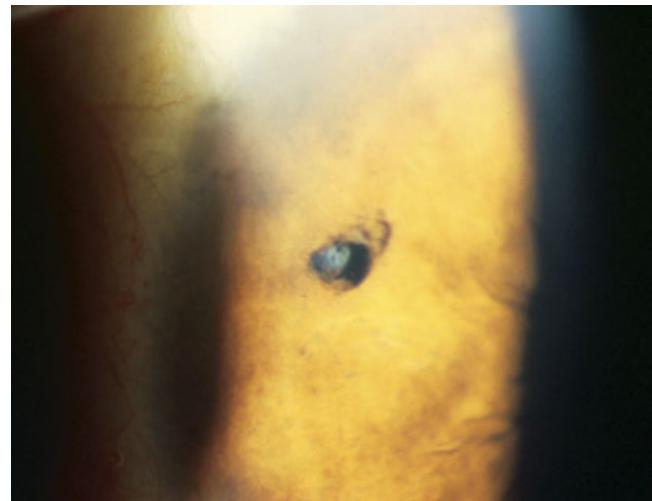


FIGURE 4I-4 Focal lens opacity beneath argon laser iridotomy.

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CYCLODESTRUCTION

Irvin P. Pollack, M.D., and John S. Pollack, M.D.

Persons with end-stage glaucoma have typically exhausted their potential for aqueous outflow and developed an elevated intraocular pressure (IOP) that cannot be controlled. In such cases, medical therapy has failed and many of these patients have undergone one or more unsuccessful filtration procedures, leading to marked scarring of the conjunctiva and extensive peripheral anterior synechiae (PAS).

Aqueous shunts (Chapter 45) have been developed to circumvent these problems. However, ophthalmologists have used an alternative technique, cyclodestruction, to reduce IOP in eyes with refractory glaucoma for more than seven decades (Table 42-1). Whereas filtration surgery and drainage devices increase aqueous outflow, the goal of cyclodestructive procedures is to reduce the rate of aqueous humor production to the point that it balances the resistance to aqueous outflow.

Initial cycloablation methods used diathermy, either applied to the ocular surface or via a penetrating approach. However, this method was abandoned due to unacceptable complication rates. For more than 30 years, cyclocryotherapy enjoyed great popularity, but it, too, was complicated by many serious risks, as well as severe postoperative pain.

The use of lasers to perform cyclodestructive procedures has gradually replaced cyclocryotherapy for the treatment of recalcitrant glaucoma. Transscleral cyclophotocoagulation (CPC) with the contact diode and neodymium:yttrium-aluminum-garnet (ND:YAG) lasers

has proved to be effective, although still unpredictable as to how well patients will respond to this treatment.

Experience with the diode laser has shown that less power and longer pulses may be associated with less tissue disruption and more effective lowering of IOP. This may be due to a better spread of the destructive thermal energy through the ciliary stroma and epithelium to reduce aqueous humor production.

Surgical intervention of any type in such eyes with end-stage glaucoma can be complicated by intraocular hemorrhage, fibrinous uveitis (sometimes with hypopyon), choroidal effusion, hypotony, phthisis bulbi, and sympathetic ophthalmia. Fortunately, such complications are relatively rare following transscleral CPC with contact lasers, and there are no reported cases of sympathetic ophthalmia using the diode laser.

In many cases, transscleral CPC compares favorably to aqueous shunts for treating all forms of refractory glaucoma. It is relatively pain-free and there is seldom any postoperative rise in IOP. Fewer postoperative visits are required, the frequency and severity of post-op complications are far less, and retention of vision is similar. Unlike cyclocryotherapy, CPC can be used in eyes with useful vision. IOP control with CPC, however, is often not as low as that seen with aqueous drainage devices.

DIATHERMY

BACKGROUND

Weve¹ found that surface diathermy could decrease IOP, but hypotony was a serious complication. Vogt² introduced the concept of penetrating diathermy, but this was sometimes complicated by corneal ulceration, hypotony, and cataract. He replaced this with partial penetrating diathermy, using electrodes that penetrated both the conjunctiva and the sclera 2.5 to 5 mm from the limbus.⁵

TABLE 42-1 EARLY CYCLODESTRUCTIVE PROCEDURES

Surface diathermy to the ciliary body	Weve ¹	1933
Penetrating cyclodiathermy	Vogt ²	1936
Cyclocryotherapy	Bietti ³	1950
Transscleral ultrasound	Coleman ⁴	1985

TECHNIQUE

Electrode needles of varying length, but usually 1.0 to 1.5 mm long, delivered a current of 3 to 45 mA for 10 to 20 sec. Two rows of diathermy burns were placed 3 to 4 mm apart over the ciliary body for one or two quadrants. The procedure was used for many years but was ultimately abandoned when it was shown to produce significant hypotony, phthisis, and cataract,⁶ as well as a low success rate.⁷

MECHANISM

The mechanism by which this procedure reduced IOP was most likely from ciliary body necrosis⁸ and hyposecretion. After each diathermy application one would frequently see aqueous oozing through the penetration site, suggesting that the more posteriorly placed applications might produce temporary drainage fistulas.

CYCLOCRYOTHERAPY

BACKGROUND

Cyclocryotherapy was first described by Bietti³ and endorsed many years later by de Roeth⁹ as a highly successful way to reduce IOP. It was easy to administer and early studies found it usually effective. It thus became the procedure of choice for cyclodestruction until later studies revealed its poor long-term success rate and serious complications.

TECHNIQUE

The procedure is performed with a nitrous oxide cryotherapy unit using a cryoprobe with a 2.5 mm tip. The tip is placed 1.0 to 1.5 mm from the corneal limbus with three or four adjacent applications made in each quadrant (Fig. 42-1). When the cryoprobe tip reaches -80°C , treatment is then timed for 45 to 60 seconds. Usually 180 to 270 degrees of circumference is treated. If three quadrants received one treatment and a second cryotherapy is required at a later time then, again, three quadrants are treated, one of which had no previous cryotherapy.

Higginbotham evaluated the effects of graded cyclocryotherapy in cats by treating one, two, or three quadrants to produce a graded destruction of the ciliary epithelium. This proportionately reduced IOP and aqueous humor production, suggesting that the treatment could be titrated to some extent.¹⁰

MECHANISM

With each application an iceball forms at the end of the cryoprobe and this extends into the ciliary body to produce cell death (Fig. 42-1). The rapid freeze produces intracellular ice crystals, and a slow thaw leads to formation of yet larger crystals that are highly destructive to the cell.¹¹ A second and later mechanism is a superimposed

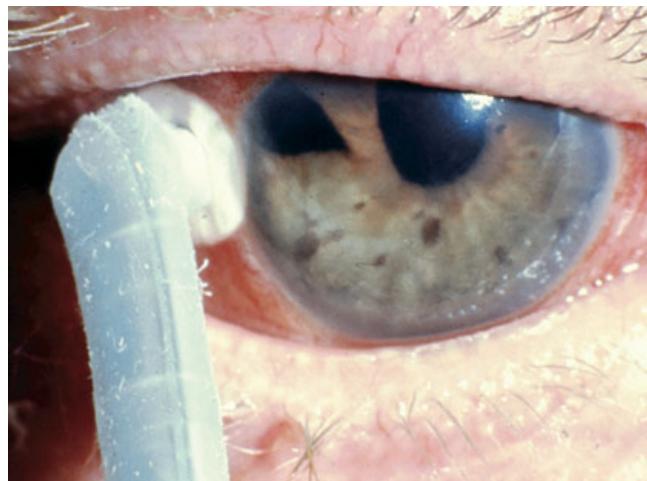


FIGURE 42-1 Cyclocryotherapy is performed by placing the cryoprobe tip 1.0 to 1.5 mm behind the corneal limbus. An iceball forms by the time the temperature reaches -80°C and produces ischemic necrosis of the ciliary body and destruction of the ciliary epithelium.

hemorrhagic infarction that results from obliteration of the microcirculation within the frozen tissue and produces ischemic necrosis.¹¹

COMPLICATIONS AND MANAGEMENT

Intense uveitis occurs in all cases, sometimes with a fibrin clot. This is best managed by frequent instillations of topical corticosteroids and cycloplegics starting on the day of surgery. Postoperative pain can be most severe during the first 24 hours. It is caused by postoperative inflammation and may be aggravated by any secondary rise in IOP. Strong analgesics as well as continued glaucoma medications, frequent topical corticosteroids, and cycloplegics will help manage these complications. Hyphema is common, especially in eyes with neovascular glaucoma (NVG), and usually clears with medical management.

Hypotony and phthisis bulbi are the most severe of the complications of cryotherapy. Brindley and Shields reported a 12% incidence of phthisis for all patients, and 22% for those with NVG.¹² Pronounced loss of vision is another serious complication of cryotherapy and Bellows recommended that cyclocryotherapy not be used unless the visual acuity was 20/200 or less.¹³

Because of these many severe complications, cryotherapy is no longer recommended for the treatment of glaucoma.

THERAPEUTIC ULTRASOUND

Focused transscleral ultrasonic radiation can produce destruction of the ciliary body in rabbit^{14,15} and human eyes.¹⁶ The mechanism by which therapeutic ultrasound reduces the IOP is presumed to be ciliary body destruction

with resulting hyposecretion. Using this technique, a transducer in a water bath is focused on the sclera over the ciliary body and three to twelve exposures of ultrasound are delivered at levels of 5 to 10 kW/cm² for 5 sec each.^{16,17} The popularity of this procedure has been limited by complications that include postoperative rise in IOP, uveitis, decreased visual acuity, scleral thinning, choroidal detachment, and phthisis bulbi.¹⁷

CYCLOPHOTOCOAGULATION

BACKGROUND

Soon after photocoagulation of the retina and iris with the xenon arc was introduced by Meyer-Schwickerath,¹⁸ it was used for transscleral CPC.¹⁹ However laser energy soon eclipsed the xenon arc as an energy source for ocular treatment and ruby and neodymium lasers were used to successfully ablate the ciliary body of rabbits through a transscleral approach.²⁰

By 1971, the argon laser was available in most large institutions, and Lee and Pomerantzeff introduced the transpupillary approach for CPC.²¹ This was best performed at the slit-lamp through a gonioscopy lens in an aphakic eye with a widely dilated pupil.²² Complications included marked uveitis and phthisis, and the reported results were variable.^{22–25}

Beckman used the ruby and Nd:YAG noncontact lasers to produce transscleral CPC.^{26,27} The results were impressive, but they, too, were variable, depending on the type of glaucoma. His best results occurred in aphakic and congenital glaucoma, with the poorest results in NVG. The instruments were large and unwieldy and required frequent adjustments and calibration. Complications of uveitis, vision loss, and phthisis were discouraging.^{28,29} This procedure is now largely replaced by contact transscleral CPC.

In 1989, Broncato and coworkers used a transscleral contact Nd:YAG laser in the thermal mode and with a bare quartz fiber tip to produce ciliary body destruction.³⁰ Since then, there have been numerous favorable reports using the contact Nd:YAG laser for CPC.^{30–34}

At about this same time, the semiconductor diode laser, originally employed for retinal photocoagulation, was used for CPC to treat glaucoma. The diode laser produces light in the 780 to 820 nm range (near infrared). This shorter wavelength has better melanin absorption than that of the Nd:YAG laser (1064 nm)³¹ and similar transmission through the sclera.^{35–37} Early studies comparing the contact diode laser to Nd:YAG suggest that the former produces more predictable and consistent lesions in human autopsy eyes³⁸ and better clinical results.³⁹

MECHANISM OF ACTION

In Dutch-belted rabbits, 1.6 J of energy delivered by contact CPC with the diode laser will produce whitening of the pars plicata, and coagulative necrosis of the ciliary

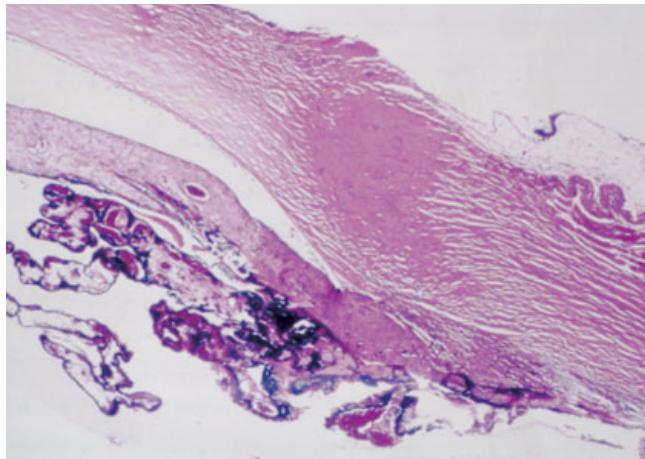


FIGURE 42-2 Histologic appearance of a rabbit eye following contact cyclophotocoagulation with the diode laser. 1.6 J of energy in Dutch-belted rabbits will produce whitening of the pars plicata, and coagulative necrosis of the ciliary epithelium and stroma.

epithelium and stroma (Fig. 42-2).^{40–42} This results in a fairly prompt reduction in aqueous production, either due to loss of the ciliary epithelium's secretory function, reduced vascular perfusion in the ciliary body, or both. There may also be selective destruction of the ciliary epithelium.^{43–44} In autopsy eyes, contact CPC with the diode laser produces thermal damage to the ciliary body^{45–47} and whitening of the ciliary processes with 2.0 to 5.0 J,⁴⁸ whereas energy levels above this will cause thermal damage to the sclera.⁴⁹

Interestingly, more posteriorly placed lesions over the pars plana or peripheral retina may also decrease IOP.^{50–51} This may be due to reduction in aqueous production caused by intraocular inflammation⁵⁰ and may be responsible for the prompt decrease in IOP that is frequently observed following CPC. Another, less likely, mechanism is increased outflow via the uveoscleral system and across the sclera.^{51–53}

PEARL... Cyclophotocoagulation reduces intraocular pressure by decreasing aqueous production, but it may also increase uveoscleral outflow.

TECHNIQUE

Anesthesia

The entire procedure may take only a few minutes, but the patient should be made as comfortable as possible. Although it may be possible to perform CPC with analgesics and topical anesthesia in a few patients,⁵⁴ this is usually ineffective. Most require a peribulbar or retrobulbar 3 to 5 mL injection of lidocaine HCl alone or in combination with bupivacaine HCl.

MEDICATIONS

Postoperative intraocular inflammation always occurs and is treated with topical 1% prednisolone acetate or hydrochloride every 1 to 2 hours while awake and atropine sulfate 1% twice daily for the first several days. The medication can then be tapered depending on the amount of inflammation. Rarely are systemic or subconjunctival steroids required for an excessive inflammatory response.

Glaucoma medications are continued right up to the time of the procedure and can be resumed the next day, if necessary. However, miotics are discontinued at least 1 day before the procedure and are not resumed as long as intraocular inflammation is present. In many cases postoperative glaucoma medications are not required because the IOP is reduced the same or next day, either due to the laser's effect on the ciliary epithelium, or due to the inflammation itself. If the latter is responsible for the reduced IOP, then the IOP will increase as the inflammation subsides. The IOP is usually checked 1 to 2 hours after the procedure, the next day, and thereafter as required.

LASERS AND SETTINGS

Contact Nd:YAG Laser

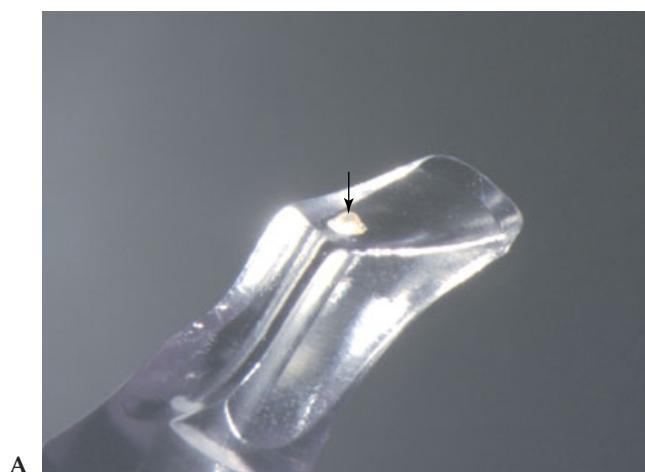
Many early studies using contact CPC were performed with the continuous-wave (cw) ND:YAG laser (Surgical Laser Technologies, Oaks, PA). Its probe delivers a cw mode of 0.1 to 1.0 sec through a 2.2 mm sapphire tip that is held perpendicular to the scleral surface.⁵⁵ Power and duration settings vary widely among investigators from about 4 to 9 W and 0.5 to 0.7 sec.^{30,31} The number of applications also varies widely. Generally, one can obtain effective results using 5 to 6 J of energy and between 30 and 40 applications.³¹

Contact Diode Laser

The diode laser system (IRIS Medical OcuLight, IRIDEX Corp, Mountain View, CA) has a maximum power output of 3.0 W and a maximum duration of 9.9 sec. The laser is compact, lightweight, portable, sturdy, and dependable. It can be used for retinal photocoagulation and trabeculoplasty as well as contact CPC. Use of the diode laser has become the preferred instrument for CPC because it produces more predictable and consistent results compared with the contact Nd:YAG laser, and with fewer complications.^{38,56–58}

The laser energy is delivered through a 600 μm diameter quartz fiber with a rounded polished tip⁵⁹ oriented by a handpiece (G-probe) and designed to deliver the laser beam 1.2 mm behind the surgical limbus with the fiberoptic approximately parallel to the visual axis (Fig. 42-3A,B). The fiberoptic tip protrudes 0.7 mm beyond the contact surface and indents the conjunctiva and sclera to enhance laser light transmission.^{35,36,60} With appropriate care the probe can be used safely for multiple applications,⁶¹ although reuse for treating humans has not yet received Food and Drug Administration approval. The probe should be cleaned after each use with an alcohol swab and checked at the biomicroscope before each use to be certain that the tip is not damaged. Carbon debris on the fiberoptic tip can produce a "hot spot" and can reduce the energy transmission through the probe, lead to damage of the probe, and cause a surface burn on the conjunctiva. Reuse of the probe for up to 20 times causes minimal decrease in energy transmission.⁶²

There are two factors that determine the laser power and duration of application: (1) the energy per application should be kept under 5 J to minimize postoperative complications, including conjunctival burns, inflammation, and hypotony; and (2) applications of longer duration allow the



A



B

FIGURE 42-3 (A) The fiberoptic tip (arrow) of the G-probe (IRIS Medical Instruments) protrudes 0.7 mm beyond the curved footplate and indents the conjunctiva and sclera during laser application. The protruding fiberoptic is located 1.2 mm behind the anterior edge of the footplate. This directs the laser beam through the sclera and into the ciliary body. (B) The probe is designed to orient the 600 μm diameter quartz fiberoptic parallel to the visual axis. The probe is placed on the sclera so that its leading edge lines up with the limbus. The curved footplate conforms to the scleral surface. [(A) Photo courtesy Iridex Corporation, Mountain View, CA]

thermal energy to spread through the tissue and reach the ciliary epithelium.

The sound of a "pop" or "snap" at the treatment site indicates tissue disruption within the ciliary body and one can titrate the power in 0.25 W increments to minimize this.⁶³ Longer applications are less likely to produce tissue disruption and more effectively reduce the IOP with fewer side effects.⁶⁴⁻⁶⁶ We have found good results with settings of 1.5 W for 2.5 to 3.0 sec (3.75 to 4.5 J), reserving the higher energy levels for repeat procedures and lower settings for eyes with more heavily pigmented irides.

Approximately 16 to 18 laser applications are evenly spaced 270 degrees around the eye over the ciliary body by aligning the side edge of the footplate with the indentation made by the footplate during the previous laser delivery. If repeat CPC is required, then another 270 degrees can be treated, including the previously untreated quadrant.⁶⁷

COMPLICATIONS

Hyperemia, Anterior Uveitis, Pain

A mild burn of the conjunctiva may occur immediately after laser treatment and usually disappears within 24 hours. This is avoided by applying mild pressure of the fiberoptic into the conjunctiva/sclera, thereby blanching the tissue. Postoperative conjunctival hyperemia and iritis with moderate cells and flare are common. Although the cells and hyperemia clear with topical corticosteroids, the flare may persist for a much longer period of time. Rarely, patients with very sick eyes, especially NVG, may develop marked postoperative anterior uveitis with sterile hypopyon or bleeding. Postoperative elevation of the IOP is rare; it may actually decrease within a few hours of treatment. Postoperative pain is also uncommon and routine analgesics are usually sufficient when the peribulbar or retrobulbar anesthesia has worn off.

Vision Loss

Until recently, cyclodestructive procedures were reserved only for eyes with poor vision potential. However, Kosoko and coworkers found that the visual acuity after diode CPC⁶⁸ was within one line of the baseline vision in 70% of patients and within two lines in 82% of patients. Other investigators have found similar results with 62 to 93% of patients having postlaser vision within two lines of the baseline visual acuity.^{67,69-76} Loss of vision may be related to the type of glaucoma and severity of the disease. This is more common in patients with NVG, and in eyes with longstanding intractable glaucoma and poor preoperative vision.

PEARL... In one study, visual acuity after CPC with the contact diode laser was within two lines of baseline in 82% of patients and within one line in 70%.

Phthisis, Hemorrhage, Sympathetic Ophthalmia

Hypotony⁷⁷ and phthisis bulbi^{72,78,79} have rarely been reported following contact CPC. Other possible complications include choroidal effusion with flat anterior chamber, vitreous hemorrhage, and cataracts. Several cases of sympathetic ophthalmia (SO) have been reported following CPC using the contact Nd:YAG laser⁸⁰⁻⁸³ but none with the diode laser.

Perforation Through Thinned Sclera

Under certain circumstances the sclera may be scarred or unusually thin. This may occur in progressive (high) myopia and at the site of previous operations. In autopsy eyes with thinned sclera, damage to the ciliary epithelium and stroma occurs with half the laser energy required to produce a similar result in an eye with normal sclera.⁸⁴ In rare cases, scleral perforation has occurred with treatment over thinned sclera,^{67,85,86} but this complication can be avoided by decreasing the energy dose.⁸⁷

CLINICAL APPLICATION OF CONTACT CPC

Refractory Glaucoma

Contact CPC with both the Nd:YAG³⁰⁻³⁴ and diode^{39,67,68,72,73,79,88,89} lasers can effectively lower IOP in patients whose glaucoma cannot be controlled by medical therapy, trabeculoplasty, or conventional filtration surgery. Because it can be used in eyes that still have useful vision, some investigators have even considered CPC for primary therapy when medical and surgical health care resources are scarce.^{57,90}

In one multicenter study, 30 eyes of 30 patients were followed for a median of 2 years after performing trans-scleral CPC with the diode laser using the G-Probe. Seventeen to 19 applications were made over 270 degrees with 2-sec duration and 1500 to 2000 mW power. The IOP fell from a mean baseline pressure of 36.1 mm Hg to a mean of 21.6 mm Hg and remained essentially unchanged for the duration of the study. The cumulative probability of success (20% decrease in IOP and final $IOP \leq 22$ mm Hg) was 72% at 1 year and 52% at 2 years.⁶⁸

If there is less reduction in IOP than needed, then the procedure can be repeated and, in some cases, three or more treatments may be required before achieving adequate pressure control. However, each retreatment carries an increased risk for bleeding, hypotony, and phthisis. CPC has been used to treat patients with painful blind eyes,⁹¹ malignant glaucoma (aqueous misdirection),⁹² and uveitic glaucoma.⁹³

Glaucoma of Childhood

Childhood glaucomas include infantile (congenital) glaucoma, juvenile-onset glaucoma, and aniridia with glaucoma.

Essentially a surgical problem, these children are usually treated by goniotomy, trabeculotomy, and trabeculectomy. However, many fail to respond to conventional surgical management. Contact CPC with the Nd:YAG⁹⁴ and diode lasers⁹⁵ has proved to be helpful in management of these cases, although the success rate is lower than with adult glaucomas. CPC for pediatric glaucoma will produce a success rate of 50 to 75%, but two to three treatments are usually required.⁹⁴⁻⁹⁷

Neovascular Glaucoma

NVG (Chapter 21) results from the development of a fibrovascular membrane over the trabecular meshwork, eventually causing closure of the anterior chamber angle by PAS.⁹⁸ Although timely panretinal photocoagulation (PRP) may prevent or halt the progression of angle neovascularization in many cases,⁹⁹ progression to angle closure sometimes occurs. Following adequate PRP, standard trabeculectomy with adjunctive antimetabolites can successfully control the IOP in many cases.¹⁰⁰⁻¹⁰² Unfortunately, filtering procedures and aqueous shunts in eyes with NVG have shown high long-term failure rates.^{101,103-105}

Transscleral diode CPC is an effective treatment for NVG and can produce reductions in IOP from 58 to 72%.^{73,106,107} Oguri et al¹⁰⁸ compared transscleral diode CPC with cw Nd:YAG CPC and free-running mode Nd:YAG CPC in the treatment of 39 consecutive eyes with NVG. In this study, the IOP control probability using the diode laser was higher than with the cw YAG and was as effective as free-running YAG. Improvement or preservation of visual acuity occurred in 76% of patients using diode laser, 44% using free-running YAG, and 56% using cw YAG. One eye in the cw YAG group had phthisis bulbi 6 months later, but neither phthisis bulbi nor any other severe complications were observed in the diode laser group. Patients receiving diode laser treatment reported significantly less pain than the other two groups. Fifteen percent of the diode laser-treated eyes developed anterior chamber fibrin.

Glaucoma After Penetrating Keratoplasty

Chronic glaucoma follows penetrating keratoplasty (PKP) in 10 to 35% of cases and is a particular risk following keratoplasty in pseudophakic eyes (Chapter 28). It is often caused by extensive PAS and can be very difficult to control medically. The elevated IOP may not only damage the optic nerve; it is also associated with a high incidence of graft failures.

When medical management and filtration surgery fail, a filtration device is often used. However, the long period of morbidity and high complication rate with aqueous shunts has been discouraging. Furthermore, graft rejection can occur in 40 to 45% of cases.¹⁰⁹⁻¹¹¹

Recent work with CPC to treat intractable glaucoma that follows PKP has produced mixed results. Early experience with the noncontact Nd:YAG laser found that

the IOP could be controlled (≤ 21 mm Hg) in 65 to 77% of cases, but 37 to 44% of eyes developed graft failure.¹¹²⁻¹¹⁴ There is little experience with the contact diode laser in treating post-PKP glaucoma. Yap-Veloso et al. successfully controlled IOP in six of 10 such eyes (IOP ≤ 21 mm Hg and $> 20\%$ decrease in IOP).⁷³ One eye developed corneal rejection that did not begin until 5 months after the CPC.

Contact Cytophotocoagulation versus Aqueous Shunts

CPC with the contact laser and implantation of an aqueous shunt can both effectively lower the IOP. Some eyes that receive an aqueous shunt have better IOP control but are prone to develop more serious postoperative complications.^{115,116} In a retrospective cohort analysis using Medicare data, it was found that eyes with an aqueous shunt were 3.8 times more likely to have an adverse outcome than eyes with a cyclodestructive procedure (95% confidence level).¹¹⁷

SPECIAL CONSIDERATION

Eyes with an aqueous shunt are 3.8 times more likely to have an adverse outcome than eyes with a cyclodestructive procedure.

CYTOPHOTOCOAGULATION WITH THE ENDOLASER

Shields and coworkers first described endoscopic CPC as a technique to apply argon laser energy to individual ciliary processes under direct visualization.¹¹⁸ This proved to be an effective way to reduce IOP, but was limited to treatment of aphakic eyes through a limbal approach, or in combination with a vitrectomy and lensectomy through the pars plana.^{119,120} Uram has developed an ophthalmic laser microendoscope that housed fiber optics for a video monitor. This delivers diode laser photocoagulation and illumination with a 20-gauge probe, and simultaneous viewing with a video camera, recorder, and television monitor.¹²¹ It was used in patients in whom a vitrectomy and lensectomy had been previously performed and provided favorable results. This technique has also been used in phakic eyes.^{122,123}

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SECTION VII

SURGICAL THERAPY OF GLAUCOMA

FILTRATION SURGERY

Allan E. Kolker, M.D.

Filtration surgery is indicated when medical management fails to provide adequate control of intraocular pressure (IOP). In recent decades, trabeculectomy, which involves removal of a block of limbal tissue beneath a scleral flap, has gained wide acceptance as an effective pressure-lowering procedure that minimizes the complications common to the earlier full-thickness techniques. The more recent addition of antimetabolites has significantly improved the success of trabeculectomy in patients at high risk for surgical failure, and has also improved our ability to provide maximal pressure lowering. Careful attention to preoperative preparation of the patient, intraoperative steps of the procedure, and postoperative management are all essential to achieving the goal of significant IOP reduction with minimal complications.

BACKGROUND

For the first two thirds of the 20th century, filtration surgery consisted of a full-thickness limbal sclerectomy beneath a conjunctival flap. Sclerectomy techniques included thermocautery, trephination, and punch forceps, all combined with an iridectomy.¹⁻⁴ All of these procedures were performed using only 2.5X magnifying operating loupes, and conjunctival closure with 6-0 silk or catgut sutures.

The postoperative course of these procedures was often difficult, and there were frequent complications. Excessive filtration, with a shallow or flat anterior chamber, was the rule and it was often said that the absence of a postoperative flat chamber would usually lead to failure. Because corticosteroids were unavailable until the 1950s, many eyes developed severe inflammation, along with cataracts and corneal decompensation. Subsequent cataract surgery was often difficult, requiring intracapsular surgical techniques through a small pupil with poste-

rior synechiae, a common result of long-term use of miotics. Although many eyes did achieve a low IOP, the blebs were usually thin and cystic, with a high risk of blebitis and endophthalmitis.

It is not surprising that many ophthalmologists approached glaucoma surgery with trepidation, sometimes following patients for long periods with gradually deteriorating visual fields before recommending surgery. However, patients with successful filtering surgery often retained stable visual fields and reasonable vision for many years.

Trabeculectomy marked a major advance in glaucoma surgery.^{5,6} This involved the removal of a partial thickness block of limbal tissue containing trabecular meshwork, sclera, and cornea under a lamellar scleral flap. Closure of the scleral flap controlled the egress of aqueous humor and reduced the major early postoperative complications associated with full-thickness procedures.⁷ Subsequent addition of antimetabolites improved the outcome of trabeculectomies in high-risk eyes, but not without their own complications.

PREOPERATIVE CONSIDERATIONS

CLINICAL INDICATIONS

Filtration surgery is indicated when the IOP is too high in spite of maximal tolerated glaucoma medications. With the recent explosion of available medications, "maximal" medications could mean four, and sometimes five different drugs. The decision of whether to surgically lower IOP in this situation is up to the patient and surgeon, after carefully weighing the potential benefits and risks of surgery against the risks and economic impact of using so many medications.

Increased interest in aggressively reducing pressure to the low teens and high single digits will likely increase

the use of filtration surgery, particularly in conjunction with antimetabolites. Although trabeculectomy is generally the procedure of choice, patients with excessive conjunctival scarring may require an aqueous shunt or cyclophotocoagulation even though the ultimate pressure control may not be as good and the complication rate can be high.

PREOPERATIVE MANAGEMENT

Chronic glaucoma medications, particularly those that produce conjunctival hyperemia, such as occurs with local allergy, should be discontinued 1 to 2 weeks prior to surgery, as this may encourage scarring and bleb failure.^{8,9} Topical steroids may help reduce surface bleeding during surgery, along with a topical vasoconstrictor, such as apraclonidine or phenylephrine, immediately before the surgery.

Long-acting indirect miotics, such as echothiopate iodide (Phospholine iodide), used now primarily in aphakic or pseudophakic eyes, may be associated with a marked postoperative surgical reaction and should be discontinued. Although chronic glaucoma medications, even without allergy, may also be associated with bleb failure, it may not be possible to discontinue all of these sudden to minimize the extent of prepare a postoperative pressure drop. Because of the need to conjunctival flap and perform an iridectomy, patients should be advised to stop using aspirin products and nonsteroidal anti-inflammatory drugs for 7–10 days prior to surgery. Discontinuing these medications, as well as anticoagulants, should always be done in consultation with the patient's primary care physician.

SURGICAL TECHNIQUE

ANESTHESIA

Although some patients require general anesthesia, most will tolerate local retrobulbar anesthesia with parenteral sedation. Some surgeons prefer additional akinesia of the orbicularis oculi. A common local anesthetic is a 1:1 mixture of 0.75% bupivacaine, which lasts up to 6 hours, and 2% lidocaine, which has a rapid onset. The addition of 150 units of hyaluronidase, if available, improves the distribution of the anesthetic and provides a more rapid anesthetic effect.¹⁰ Peribulbar anesthesia may be a suitable substitute but requires a large injection volume, which may increase pressure on the globe. More recently, some surgeons have begun using superior sub-Tenon's anesthesia injection, and in some instances, topical anesthesia.^{10a}

CONJUNCTIVAL FLAP

A superior rectus bridle suture can be used to rotate the globe down and expose the superior limbus and conjunctiva. However, many surgeons who use a limbus-based conjunctival flap find that a 6-0 silk suture placed in the

superior cornea, about one half corneal thickness and parallel to the limbus, often provides better exposure for subsequent conjunctival closure and avoids trauma to the superior rectus.

Many surgeons prefer a limbus-based conjunctival flap because it allows a secure closure, with less chance of leakage shortly after surgery. A fornix-based flap is easier to dissect and close, with less chance of creating a buttonhole. However, these are more likely to leak, and thus restricts the early use of massage. Long-term IOP control for both approaches appears to be comparable.^{11–13}

CONTROVERSY

A limbus-based conjunctival flap allows a secure closure, with less chance of leakage, whereas a fornix-based flap is easier to dissect and close.

For a limbus-based flap, the incision should be made down to the sclera, 8 to 10 mm superior to the limbus, either nasal or temporal to the superior rectus muscle tendon (Fig. 43–1A). Many surgeons prefer the superior nasal quadrant, reserving the temporal approach for possible later cataract surgery, away from the bleb, or for a subsequent trabeculectomy, should this become necessary. However, clear cornea cataract techniques make this a less important consideration and a superior or superior temporal location is less likely to result in an uncomfortable nasal bleb. When faced with scarring, a subconjunctival injection of balanced salt solution (BSS) can elevate the tissues and help the surgeon identify the best site for surgery.

Following a 7 to 10 mm incision, the combined conjunctival and Tenon's flap is bluntly dissected up to the limbus, exposing about 5 mm of the corneoscleral sulcus. The reflecting strands of Tenon's capsule are scraped anteriorly with a spatula or curved blade. Removing Tenon's does not appear to affect the long-term pressure control.¹⁴ Most surgeons now preserve Tenon's to help prevent wound leaks, especially when using releasable sutures and antimetabolites.

Fornix-based flaps are created by incising conjunctiva and Tenon's capsule for 5 to 6 mm at the limbus, and establishing a plane at the level of episclera. Small, radial relaxing incisions at each end may facilitate exposure.

SCLERAL FLAP

Following light, wet-field cautery to the sclera, the scleral flap should be created about 4 mm wide at the limbus. It may be semicircular or rectangular, extending 2 to 3 mm posteriorly; triangular, measuring 4 mm per side; or trapezoidal, with a 2-mm height and narrowing to 3 mm wide at the apex (Fig. 43–1B). The flap shape has no apparent effect on ultimate pressure control. The flap,

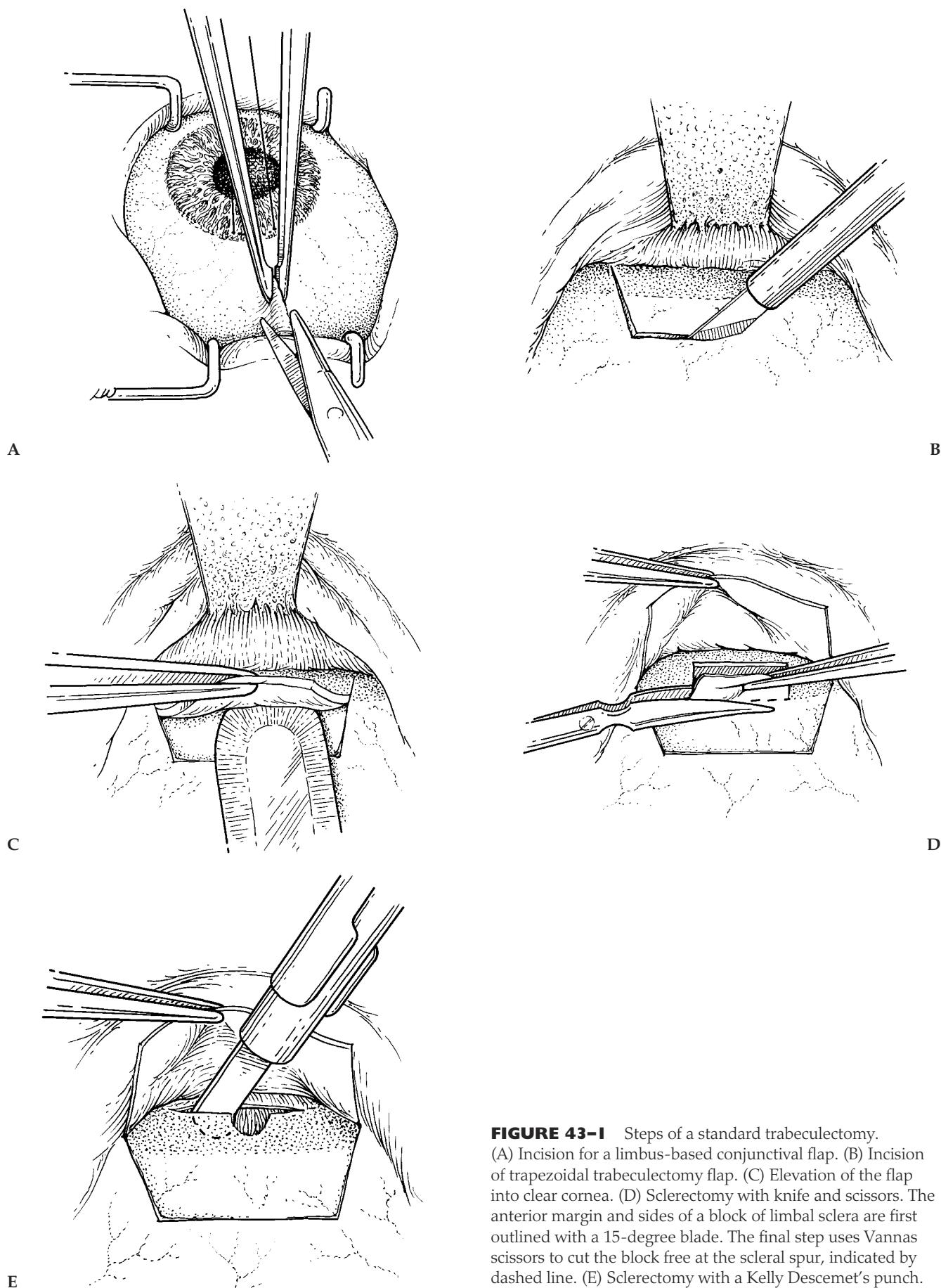


FIGURE 43-1 Steps of a standard trabeculectomy.
(A) Incision for a limbus-based conjunctival flap. (B) Incision of trapezoidal trabeculectomy flap. (C) Elevation of the flap into clear cornea. (D) Sclerectomy with knife and scissors. The anterior margin and sides of a block of limbal sclera are first outlined with a 15-degree blade. The final step uses Vannas scissors to cut the block free at the scleral spur, indicated by dashed line. (E) Sclerectomy with a Kelly Descemet's punch.

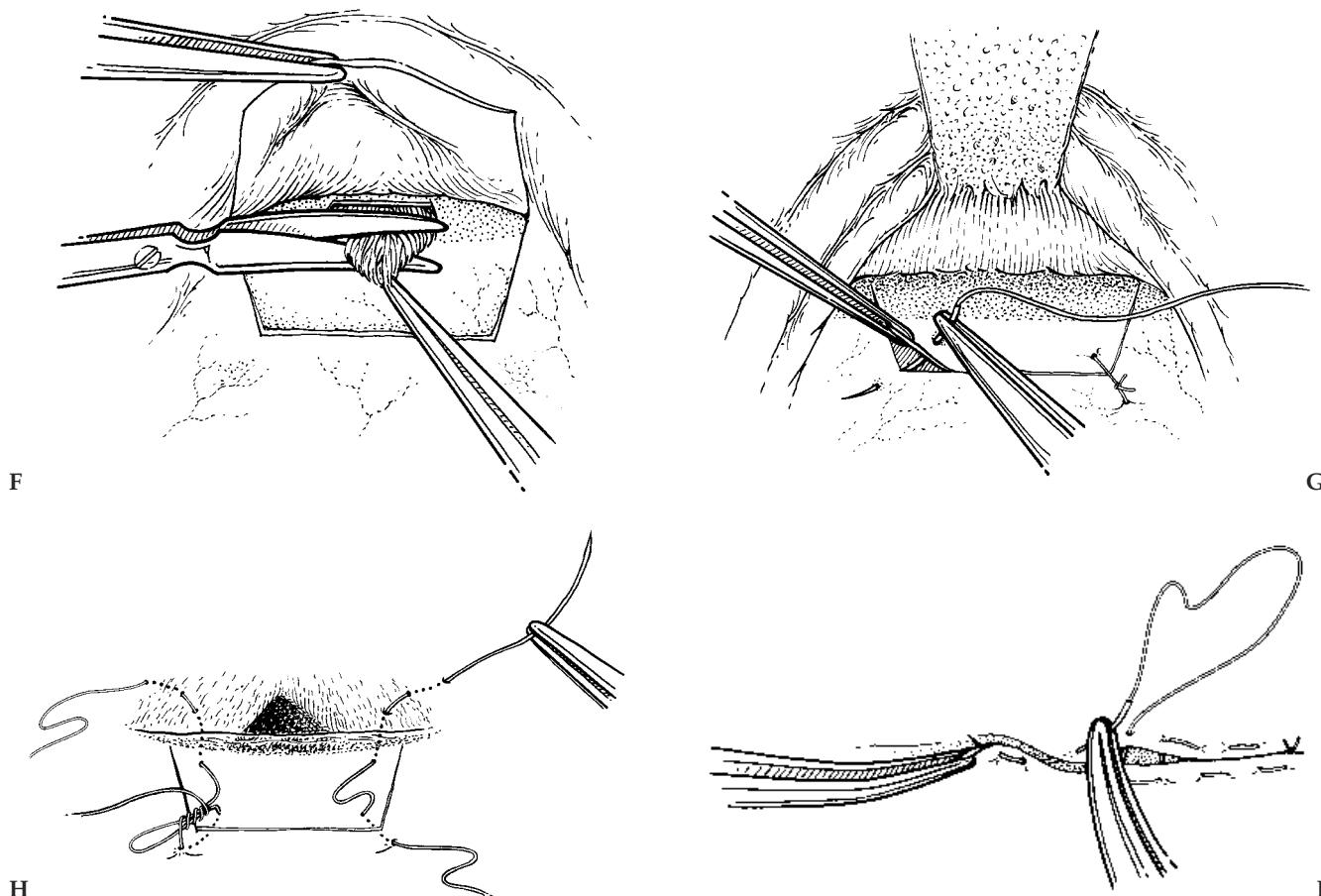


FIGURE 43-1 (F) Peripheral iridectomy. (G) Scleral flap closure with interrupted sutures. (H) Scleral flap closure with releasable sutures. (I) Technique of conjunctival closure of a limbus-based flap using a running horizontal mattress technique.

outlined with perpendicular cuts using a super sharp or diamond blade, should be about one half scleral thickness and then elevated into clear cornea with a spatula knife, so that iris is visible through the peripheral cornea (Fig. 43-1C). Alternatively, surgeons comfortable with phacoemulsification may prefer to make a 4 mm groove 3 mm posterior to the limbus and undermine toward the cornea with an angled spatulated knife, cutting the sides of the flap anteriorly up to the limbus at either margin of the scleral tunnel (Chapter 44, Fig. 44-1F).

A paracentesis is made superotemporally in clear cornea using a 15-degree sharp blade oriented parallel to the iris. This allows subsequent reformation of the anterior chamber, either during the procedure or postoperatively with balanced salt solution or viscoelastics. Most surgeons will apply antimetabolites, discussed in the following text, prior to the sclerectomy.

SCLERECTOMY

The sclerectomy, or fistula into the anterior chamber, can be created either with a combination of the 15-degree blade and Vannas scissors (Fig. 43-1D), or with a Kelly Descemet's punch (Fig. 43-1E). In the former, the sur-

geon outlines the sclerectomy with the blade, and then enters the anterior chamber (Fig. 43-1D). To reduce the risk of iris prolapse, vertical cuts at the lateral edges are made first, followed by an incision through the anterior, horizontal margin of the fistula. Keeping the tip just inside the anterior chamber, with the sharp edge pointing up, and cutting in an upward, horizontal direction allows the surgeon to make an accurate cut. This may be necessary in either direction to ensure that Descemet's is completely incised across the entire block, freeing it on three sides. With the assistant elevating the scleral flap with a Colibri-type forceps, the surgeon then cuts the block completely free at the scleral spur. This is most easily performed with Vannas scissors, using a vertical cut to avoid leaving a shelf of Descemet's membrane, which could occlude the sclerectomy. Iris stroma detail should now be clearly visible.

When using the Kelly Descemet's punch, the surgeon begins with an anterior horizontal incision, and then inserts the tip of the punch into the anterior chamber, followed by removing several pieces of tissue posteriorly (Fig. 43-1E). With this technique, it is not necessary for an assistant to hold the scleral flap during this delicate part of the procedure.

SPECIAL CONSIDERATION

The Kelly Descemet's punch allows the surgeon to create the sclerostomy without relying on an assistant to hold the scleral flap.

With either technique, injecting a viscoelastic into the anterior chamber may help protect the iris and lens from injury while making the knife incisions, and may reduce the incidence of postoperative flat anterior chamber.¹⁵ The sclerectomy should measure about 2 to 3 mm by 1 mm, with the lateral edges placed 0.5 to 1 mm from the sides of the scleral flap. Unwanted iris prolapse into the sclerectomy can be managed by making a small radial cut with Vannas scissors in the bulging iris, which allows the iris to retract into the anterior chamber. Bleeding from the cut edge of the sclerectomy, which is common with excessive use of the Kelly punch posterior to the scleral spur, can be controlled with light wet-field cautery. Cutting too far posteriorly can also produce a cyclodialysis leading to prolonged hypotony.

IRIDECTOMY

A peripheral iridectomy prevents iris incarceration in the fistula. If the pupil is dilated, intracameral injection of acetylcholine (Miochol) will constrict the pupil and facilitate a basal iridectomy without causing conjunctival hyperemia. With the assistant retracting the scleral flap with either a forceps or cellulose sponge, the surgeon orients the iris scissors parallel to the limbus and grasps the iris near its base with fine forceps, which by now is often prolapsing through the fistula. Gently pulling the iris away from the scissors for the beginning of the cut and toward the scissors for the completion of the cut produces an iridectomy that is wider than the sclerectomy (Fig. 43–1F). A curved Vannas scissors, held with the curve toward the limbus, provides excellent access to the iris root and a basal iridectomy. Care is necessary to avoid tearing the iris at its insertion or including ciliary processes in the iridectomy, as both will cause profuse bleeding.

To avoid inadvertent lens and zonule injury, the surgeon should not reach inside the eye to grasp iris. In eyes without spontaneous iris prolapse, gentle pressure with the scissors posterior to the sclerectomy can encourage the iris to bulge slightly through the fistula. After the iridectomy, the surgeon should inspect the sclerectomy to ensure that iris tissue is completely removed. Iris bleeding will usually stop following gentle irrigation with balanced salt solution or, occasionally, injection of viscoelastic.

SCLERAL FLAP CLOSURE

Rectangular or trapezoidal flaps are closed with an interrupted 10-0 nylon suture at each corner (Fig. 43–1G), and triangular flaps with a suture at the apex and one along

each margin. All knots are trimmed and rotated into the sclera. Filling the anterior chamber with BSS through the paracentesis, the surgeon can then test the flap closure. The anterior chamber should remain formed, with only a slow leak at the flap margins that increases easily with light pressure behind the flap. If the anterior chamber shallows spontaneously, additional flap sutures are necessary. The surgeon should never leave the operating room if the anterior chamber cannot be easily deepened or does not retain fluid.

PITFALL... The surgeon should never leave the operating room if the anterior chamber cannot be easily deepened or does not retain fluid.

Surgeons have described several types of releasable sutures.^{16,17,17a} In one,¹⁷ the suture is passed backhand through the sclera and up through the posterior edge of the scleral flap. The needle is then passed back into the scleral flap more anteriorly, beneath the conjunctival insertion, to exit in clear cornea. This leaves a loop on top of the scleral flap (Fig. 43–1H). The needle is then passed through superficial cornea either nasally or temporally to stabilize the loose ends. A single tie, using four throws of the proximal end of the suture, is then made around the loop on top of the scleral flap and pulled tight. Postoperative removal of this suture involves freeing its corneal end at the slit-lamp and then pulling downward. This pulls the loop out of the knot and frees the entire suture.

CONJUNCTIVAL CLOSURE

The increased popularity of intraoperative and postoperative antifibrotic agents requires meticulous, watertight closure of the conjunctival incision. For limbus-based conjunctival flaps, a two-layer closure of Tenon's and conjunctiva, using a running 9-0 Vicryl or 10-0 nylon suture with a lock every 3 to 4 bites, is unlikely to leak. Some surgeons prefer a running horizontal mattress technique, either in a double layer or a single layer closure that incorporates Tenon's capsule (Fig. 43–1I). Using vascular, tapered needles, as opposed to cutting or spatula needles, minimizes conjunctival holes. After closure, intracameral injection of BSS via the paracentesis should also fill the bleb (sometimes requiring light pressure adjacent to the scleral flap), and the wound can be checked either by direct inspection or by "painting" the suture line with a moistened fluorescein strip.

Fornix-based flaps are closed by suturing the edges of conjunctiva to the limbus, pulling the anterior margin taut over the cornea, and closing any gaps at the margins with additional sutures.^{18,19} Many surgeons will also pull the anterior edge of the conjunctiva down to the cornea with mattress sutures. Attaching the edge of the conjunctiva to the peripheral cornea or a skirt of limbal conjunctiva with a running horizontal mattress suture is also very effective.

POSTOPERATIVE MANAGEMENT

POSTOPERATIVE MEDICATIONS

Bleeding and inflammation, which can lead to episcleral and flap fibrosis, present the greatest threat of failed filtration. The best treatment for hemorrhage is meticulous control of bleeding during the surgery. This includes light wet-field cautery of episcleral vessels along the outline of the scleral flap, and point cautery to bleeding from the flap margins, avoiding tissue retraction. Bleeding from an iris process or torn iris base following the iridectomy may also be controlled with point cautery, or, if necessary, 1% nonpreserved epinephrine on a cellulose sponge.

Antibiotics and corticosteroids are usually administered at the conclusion of surgery, either as a subconjunctival injection or soaked into a collagen shield.²⁰ Prednisolone drops, begun on the first day after surgery, are used every 2 hours during waking hours for at least 2 weeks, and then tapered over the next 4 to 8 weeks. Topical antibiotics are generally used two to four times per day for 2 weeks, or until removal of releasable sutures.

By relaxing the ciliary muscle and pupillary sphincter, cycloplegics improve patient comfort, deepen the anterior chamber, and reduce miosis and the risk of posterior synechiae. Topical 1% atropine is usually instilled at the end of surgery and then used once or twice daily for about 2 weeks, or until inflammation is resolved. Because frail, elderly patients can become confused and disoriented even with this dosage, homatropine may be safer.

PRESSURE MANAGEMENT IN THE EARLY POSTOPERATIVE PERIOD

Abrupt lowering of IOP following a trabeculectomy may lead to a flat chamber and hypotony. To minimize these risks, and because judging the exact suture tension at the time of surgery is always difficult, many surgeons will place extra interrupted sutures in the scleral flap, to be cut later by laser, or releasable sutures that can be removed postoperatively at the slit lamp.

Laser suture lysis is performed by blanching and compressing the overlying bleb on the suture with either a Hoskins suture lysis lens or the edge of a Zeiss goniolens.²¹ Typical laser settings are 50 to 100 µm spot size, 0.1 sec duration, and 200 to 500 mW power. Slight pressure at the edge of the scleral flap may help form the bleb, if it does not form spontaneously. Although topical vasoconstrictors may reduce the risk of bleeding, subconjunctival blood and thick, fibrotic, or edematous tissue may make it difficult to visualize and cut the suture.

Complications of laser suture lysis include hypotony, especially if more than one suture is cut, and damage to the conjunctival flap. Subconjunctival blood may absorb the laser energy, resulting in a conjunctival burn or perforation. Using red wavelength laser energy with a dye laser may minimize this risk. Excessive energy, repeated laser applica-

tions, and improper focus can also perforate the conjunctiva. Use of releasable sutures avoids those problems.

Complications of releasable sutures include intraoperative laceration or tearing of the anterior base of the scleral flap during passage of the needle into the cornea. This is minimized by making the flap at least one third scleral thickness. Other complications include conjunctival buttonhole and injury to the lens and corneal endothelium if the needle is passed too deeply into the anterior chamber. Postoperatively, the externalized suture presents a potential wick for bacteria to enter the bleb, and blebitis, endophthalmitis, and corneal ulceration have all been reported in eyes with exposed releasable sutures.

The timing of laser suture lysis and removal of releasable sutures is highly individualized. Neither should be performed in the first day or two after surgery if the pressure can be reduced with massage and viscoelastic material remains in the anterior chamber. Following this, lysis or removal can be performed with good effect up to 2 weeks after surgery, when the chamber is deep and the IOP at least 8 to 10 mm Hg. Beyond this, releasable sutures may become fibrosed and difficult to remove, often breaking off at the corneal surface. However, antimetabolites can greatly extend the time for effective suture release.²²

ANTIMETABOLITES

Intraoperative and postoperative antimetabolites have greatly improved the results of filtration surgery in eyes at high risk for surgical failure (Table 43–1).^{23–31} When used in primary trabeculectomies, 5-fluorouracil (5-FU) and mitomycin-C can achieve pressures significantly lower than those seen without antimetabolites.^{32–35} However, the risk of complications causes many surgeons to avoid mitomycin C in this setting, whereas others simply prefer intraoperative 5-FU.

5-FLUOROURACIL

5-Fluorouracil (5-FU) is a fluorinated pyrimidine antagonist that inhibits fibroblast proliferation by suppressing the DNA synthesis enzyme thymidylate synthetase and by interfering with RNA processing.³⁶ It may also disrupt fibroblast migration through its intracellular metabolite, 5-fluorouridine, an inhibitor of fibroblast contraction.

TABLE 43-1 HIGH RISK FACTORS FOR FILTRATION FAILURE

Young age
Black race
Previous failed filtration surgery
Aphakia and pseudophakia
Neovascular glaucoma
Inflammatory glaucoma

5-FU may be administered as a series of 5 mg injections during the first 2 weeks after surgery, or applied during the surgery itself. Subconjunctival injections are given over several seconds as 0.1 mL of a 50 mg/mL solution using a 30-gauge needle on a tuberculin syringe, either inferiorly or superiorly, in a quadrant adjacent to the bleb. This is followed by irrigation with BSS to reduce epithelial toxicity. A cotton pledge soaked with propracaine placed between the lid and eyeball for several minutes usually provides sufficient anesthesia. Orienting the needle bevel toward the globe to keep the injection just beneath the conjunctiva helps minimize discomfort.

When applied intraoperatively, 5-FU (50 mg per mL) is soaked on a piece of methylcellulose sponge cut to the size of the scleral flap, and placed for 3 to 5 minutes beneath the conjunctiva and Tenon's capsule, either on top of or underneath the scleral flap, and then removed. The tissues are then irrigated with BSS before completing the surgery. Postoperative 5-FU injections may be given in eyes with marked inflammation or injected blebs.

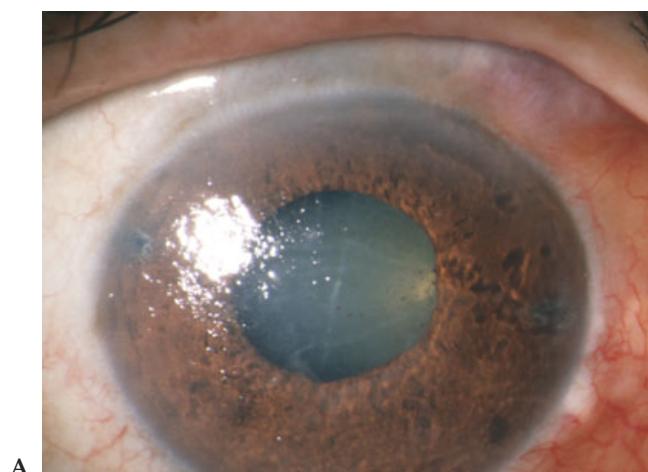
Side effects of 5-FU include wound leaks and corneal epithelial changes. Postoperative wound leaks should always be closed immediately. Although many patients develop mild punctate keratitis, large epithelial erosions

are rare, unless the patient receives more than five or six injections (Fig. 43-2A).^{26,27,37} Such erosions can take several weeks to heal as the epithelium recovers from the medication. Treatment consists of topical lubricants and reducing the frequency of corticosteroids. 5-FU injections should be discontinued if the patient develops punctate epithelial changes of the cornea or conjunctiva.

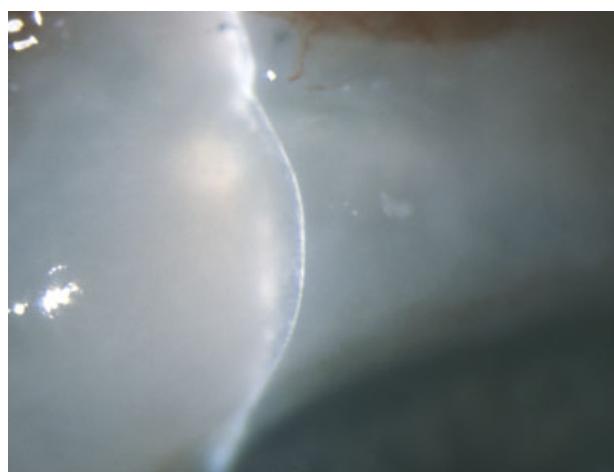
MITOMYCIN-C

Mitomycin-C (MMC), an antibiotic isolated from *Streptomyces caespitiosus*, causes crosslinking of DNA and, at higher concentrations, may inhibit RNA and protein synthesis. These antineoplastic and cytotoxic properties make it attractive for controlling the healing reaction that normally follows incisional surgery.

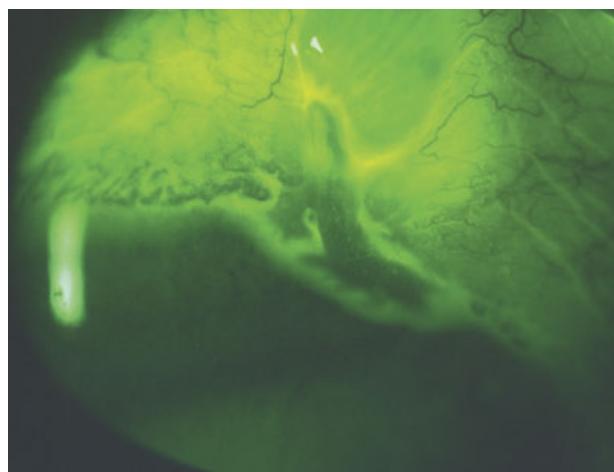
MMC is applied intraoperatively on a cellulose sponge, much as described above for 5-FU. Because this drug is very toxic to the corneal endothelium, most surgeons administer it prior to entering the anterior chamber. Used in concentrations from 0.2 to 0.5 mg/mL, for 2 to 5 minutes, it can be applied with the conjunctiva and Tenon's capsule draped over the sponge, or just to the episclera. Copious irrigation with BSS and removal of all



A



B



C

FIGURE 43-2 (A) Corneal epithelial erosion following repeated subconjunctival 5-FU injections. (B) A thin, avascular bleb increases the chance of late bleb leaks, demonstrated by (C) A positive Seidel test.

instruments touching the sponge helps minimize the risk of introducing the drug into the eye.

Histologic studies show that MMC produces an avascular and acellular bleb (Fig. 43–2B,C). The complications of this drug are more frequent and severe than with 5-FU, and the incidence of wound complications and large, avascular cystic blebs is directly related to the concentration and duration of application. Many surgeons prefer concentrations of 0.2 mg/mL, and durations of 2 minutes, decreasing the duration and concentration in patients with thin conjunctiva, or increasing these parameters in eyes with thick Tenon's capsule or significant prior scarring. Late bleb complications, such as leaks, infection, hypotony, and maculopathy are all more common with MMC.³⁸

Intraoperative use of antimetabolites prolongs the time that suture lysis or releasable suture removal can improve post-op bleb function. When such agents are used, suture removal or lysis is unusual before 3–6 weeks postoperatively.

COMPLICATIONS

Intraoperative complications, mostly in the form of trauma to the conjunctiva and scleral flap, may significantly affect the ultimate success of filtering surgery, particularly if they restrict the use of antimetabolites. Post-operative complications may occur early, within days or weeks, or late, at anytime thereafter (Table 43–2).

INTRAOPERATIVE COMPLICATIONS

Subconjunctival blood from a large retrobulbar hemorrhage following local anesthesia complicates the dissection and increases inflammation, scarring, and the chance

of bleb failure. In this situation, surgery should be postponed until the blood clears.

Conjunctival buttonholes occur periodically, especially in elderly patients with very thin conjunctiva, prior surgery, and scarring. If a large buttonhole develops early in the operation, the surgeon should select an adjacent site for the procedure. Small buttonholes can be closed with an interrupted 10-0 nylon suture on a vascular needle, incorporating Tenon's when possible. Buttonholes near the limbus are best managed by excision and suturing the anterior conjunctival edge to the limbus with a mattress suture, following epithelial debridement.

Shrinkage of the scleral flap from excessive cautery can be avoided by using a point tip wet-field cautery, or, in stubborn cases, topical epinephrine on a sponge. If shrinkage does occur, the surgeon should meticulously close the flap to prevent excessive drainage. Tearing or complete avulsion of the flap generally results if the flap is too thin or if excessive traction is used during the dissection. Tears can sometimes be repaired with a 10-0 or 11-0 nylon suture, whereas avulsion may require suturing a flap of donor sclera or pericardium over the fistula.

Iris and ciliary process bleeding may occur following the peripheral iridectomy, particularly if the iris is torn or the sclerectomy is not anterior enough. Iris bleeding typically will stop with gentle BSS irrigation. Light, point tip cautery, touching the tip to the ciliary processes prior to applying current, can shrink occluding processes and also slow bleeding. Persistent bleeding may respond to topical epinephrine.

EARLY POSTOPERATIVE COMPLICATIONS

A hyphema, usually from the iris base or ciliary processes, rarely persists for more than a few days, and surgical washout is seldom necessary. Although all glaucoma

TABLE 43-2 COMPLICATIONS OF FILTRATION SURGERY

<i>Intraoperative</i>	<i>Early Postoperative</i>	<i>Late Postoperative</i>
Retrobulbar hemorrhage	Hyphema	Filtration failure
Conjunctival buttonhole	Excessive inflammation	Episcleral fibrosis
Scleral flap shrinkage	Endophthalmitis	Encapsulated bleb
Tearing or avulsion of the scleral flap	Choroidal effusion	Cataract
Iris and ciliary process bleeding	Suprachoroidal hemorrhage	Bleb leak
Suprachoroidal hemorrhage	Deep anterior chamber with elevated IOP	Blebitis
	Internal blockage of the sclerostomy	Endophthalmitis
	Retained viscoelastics	Hypotony maculopathy
	Tight flap sutures	Dysmorphic bleb
	Shallow anterior chamber with low IOP	Central vision loss
	Conjunctival wound leak	
	Overfiltration	
	Aqueous hyposecretion	
	Iridocyclitis	
	Ciliary body detachment	
:	Inadvertent cyclodialysis cleft	
	Concurrent aqueous suppressants in fellow eye	
	Ciliary block glaucoma	

surgeries develop some degree of postoperative inflammation, topical corticosteroids and cycloplegics are usually sufficient. Sub-Tenon's depo steroids may be useful in some cases, but systemic corticosteroids are rarely necessary. Endophthalmitis in the early postoperative period is rare.

Choroidal Effusion and Suprachoroidal Hemorrhage

Choroidal effusions from low IOP are common following filtration surgery. Most resolve spontaneously as the eye pressure increases and require no specific treatment, unless they are unusually large and the retinal surfaces become apposed. However, chronic effusions can be associated with delayed suprachoroidal hemorrhage. This devastating complication is more common in aphakia and after vitrectomy.^{39,40} It is almost always accompanied by severe pain, loss of vision, high, intraocular pressure and shallowing of the anterior chamber. Although limited anterior hemorrhages can resolve without visual loss, eyes with large hemorrhages involving the posterior pole generally do poorly. Prevention remains the best treatment. This involves avoiding severe hypotony following surgery, and warning the patient to avoid vigorous physical activity, bending over, or Valsalva for the first 2 to 4 weeks after surgery.

Deep Anterior Chamber With Elevated Intraocular Pressure

This situation, usually accompanied by a low or flat bleb, strongly suggests internal blockage of the sclerostomy, retained viscoelastic material, or tight scleral flap sutures. Gonioscopy is key to identifying the cause and usually guides the surgeon to the proper management. Iris tissue incarcerated in the sclerostomy may be eliminated by shrinking the base of the iris with long-duration, low-energy applications of the argon laser. Retained lens capsule, an inflammatory membrane, or incompletely excised Descemet's membrane can be cut with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. Coagulated blood within the fistula or beneath the flap will often lyse spontaneously within 3 to 5 days.

If there is no obvious obstruction, gentle pressure at the posterior margin of the scleral flap with a cotton-tip applicator, or through the lid with the examiner's thumb, will usually elevate the bleb and lower the IOP. Viscoelastics will usually resorb in a day or two, whereas persistent, recurring elevated pressure may require suture lysis or removal of releasable sutures.

Shallow Anterior Chamber With Low Intraocular Pressure

This situation strongly suggests either a wound leak or overfiltration. In some cases, this may be further complicated by aqueous hyposecretion, particularly in aphakic and pseudophakic eyes. Hyposecretion may also result from iri-

docyclitis, ciliary body detachment, inadvertent cyclodialysis cleft during surgery, or concurrent use of topical aqueous humor suppressants in the fellow eye (Chapter 46).

Although slow leaks may close spontaneously, persistent leaks should be closed with 9-0 polyglactin or 10-0 nylon suture on a vascular needle under topical anesthesia, either at the slit-lamp or with an operating microscope. A totally flat anterior chamber due to excessive filtration with contact between the lens and cornea requires prompt surgical reformation of the anterior chamber and drainage of choroidal effusions, which commonly accompany this situation (Fig. 43-3).

Ciliary Block Glaucoma

Ciliary block glaucoma, or malignant glaucoma, is a rare complication resulting from pooling of aqueous behind the anterior hyaloid face (Chapter 28). This displaces the vitreous forward against the lens, iris, and ciliary body, shallowing the anterior chamber. Although IOP is usually elevated, the extent of the pressure rise may be mild following filtration surgery, producing a pressure that is high relative to what might be expected in this clinical situation. This complication, which is more common in small hyperopic eyes and nanophthalmos, is more likely to occur after surgery in the fellow eyes when sun in the first eye.

LATE POSTOPERATIVE COMPLICATIONS

Filtration Failure

A functioning filter typically is characterized by diffuse elevation of the conjunctiva, often with the appearance of subtle, subepithelial microcysts (Fig. 43-4A,B). Bleb failure usually results from the growth of fibrous tissue at the level of the episclera. Because this response is stimulated by inflammation, aggressive control of the inflammatory response is key to successful filtration surgery.

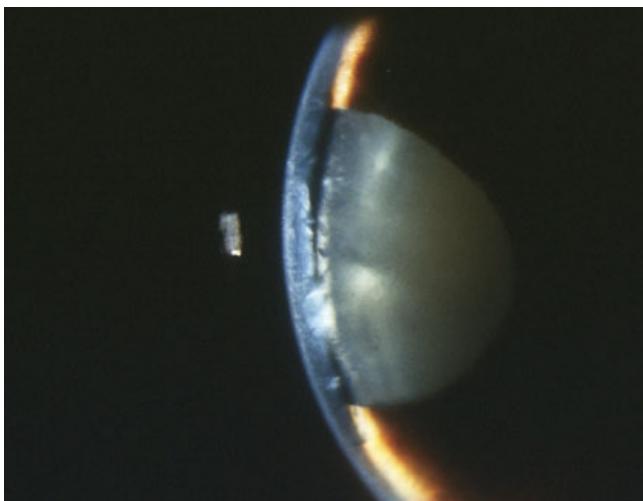


FIGURE 43-3 Flat anterior chamber with lens–cornea touch, early corneal decompensation, and cataract.

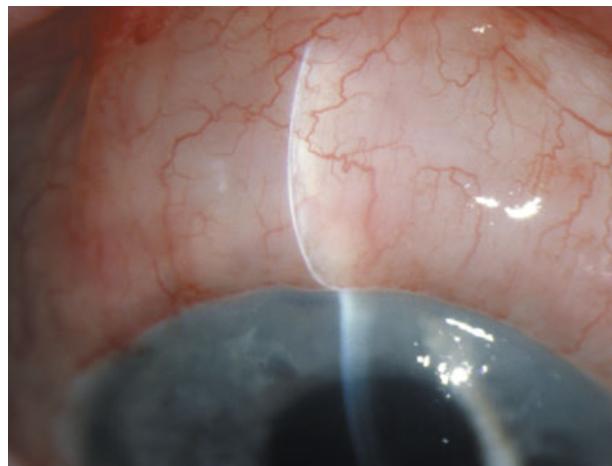
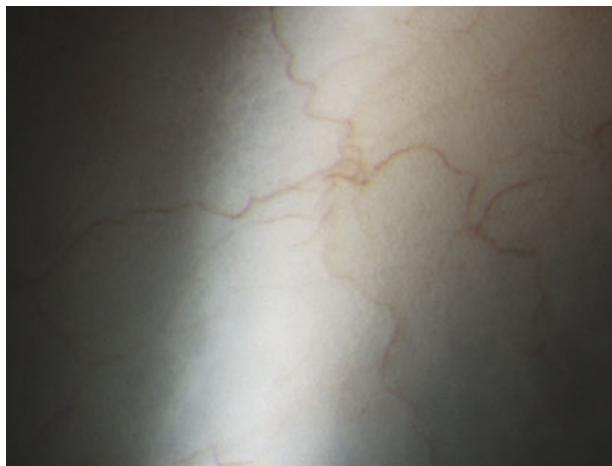
**A****B**

FIGURE 43-4 (A) Functioning filters typically display diffuse elevation of the conjunctiva, often with (B) subepithelial microcysts, best seen at either side of the slit beam.

Some cases develop a dome of fibrous tissue over the scleral flap, usually 3 to 6 weeks after surgery (Fig. 43-5A,B).^{41,42} Sometimes referred to as bleb encapsulation or a Tenon's capsule cyst, this can be accompanied by markedly elevated pressure, which may be mistaken for a steroid response. Early excision of the capsule usually leads to rapid scarring and bleb failure. However, with topical steroids and aqueous humor suppressants, a high percentage of such cysts will spontaneously thin out in time, leading to good long-term success.⁴³ Ocular "massage" is often very useful in this situation. This consists of the patient applying steady, digital pressure to either the inferior or temporal globe through the eyelids for 5 seconds, with one or two repetitions, two or three times per day.

PEARL... Encapsulated blebs will often respond in time to massage, topical steroids, and aqueous humor suppressants.

Blebs can also fail months to years after an initially successful procedure. This is accompanied by gradual collapse and thickening of the bleb, probably due to slow growth of scar tissue over the scleral flap. Others fail due to scarring of the trabeculectomy flap in the limbal bed (Fig. 43-6). Some of these cases require surgical revision of the bleb with mitomycin C. Membranous obstruction of the fistula can be treated with the argon or YAG laser, although this is generally only successful if the filter was previously functioning.^{44,45}

Eyes with encapsulated blebs that do not spontaneously function may respond to a needling procedure in conjunction with mitomycin-C. This involves topical anesthesia followed by subconjunctival injection of 0.1 mL of 1% xylocaine containing mitomycin-C, diluted to a concentration of 0.02 to 0.05 mg/mL. After 15 to 30 minutes, a 27- or 30-gauge needle on a tuberculin syringe containing lidocaine is inserted into conjunctiva several millimeters from the bleb and a small amount of lidocaine is injected.

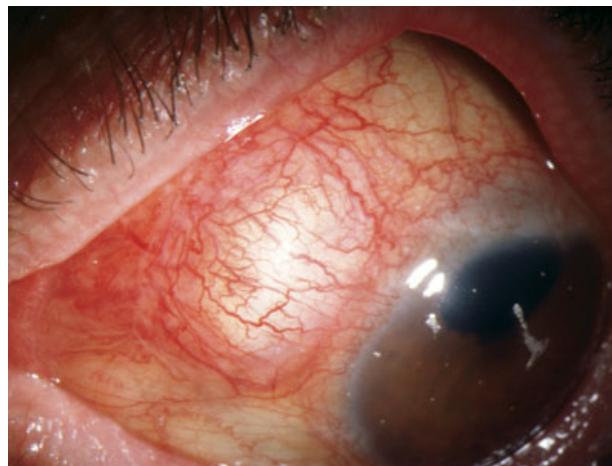
**A****B**

FIGURE 43-5 (A) Bleb encapsulation usually appears as a focal dome. Vessels deep to the conjunctival surface indicate the presence of scar tissue that forms the wall of the encapsulation. (B) Spontaneous filtration adjacent to an encapsulation several months after surgery.

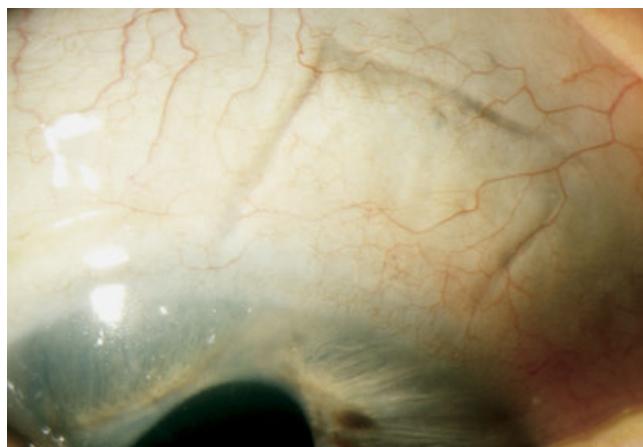


FIGURE 43-6 Failed trabeculectomy with scarring of the trabeculectomy flap into the scleral bed.

The needle is then advanced to make multiple openings in the cyst wall and then removed, followed by suturing the needle track with a polyglactin suture. Many surgeons perform bleb needling with 5PU, instead of mitomycin-C.

In cases without an obvious cyst, some surgeons will insert the needle beneath the scleral flap to elevate it from its bed, although this carries a higher risk of hemorrhage. Additional complications include hypotony, shallow anterior chamber, choroidal effusion, and even suprachoroidal hemorrhage, especially if a leak is not adequately closed.

Cataract

Cataract formation, or progression, occurs in about one third of eyes following filtering surgery.⁴⁶ Although an early cataract can result from lens trauma, flat anterior chamber, inflammation, steroid use, and marked hypotony, most develop months to years after uneventful surgery. When necessary, cataract extraction is best performed away from the bleb, by phacoemulsification through a lateral corneal incision. Because this may itself lead to bleb failure, some surgeons will give postoperative 5-fluorouracil injections in addition to intense topical steroids, although its effectiveness is not conclusive.

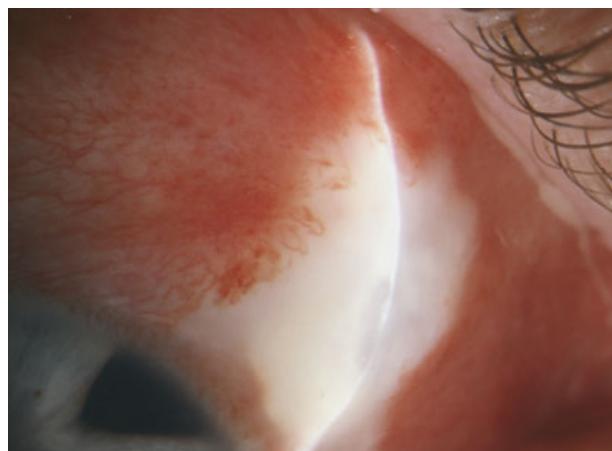


FIGURE 43-7 (A) Bleb infection, or blebitis, may progress to (B) endophthalmitis if not detected early and managed aggressively.

Late Bleb Leak

Conjunctival bleb leaks occurring months to years after surgery are usually associated with thin, cystic, avascular blebs, as already discussed. Management involves a range of maneuvers, from simple patching or suturing to full excision of a thin, necrotic bleb with advancement and closure of adjacent conjunctiva (Chapter 46).

Blebitis and Endophthalmitis

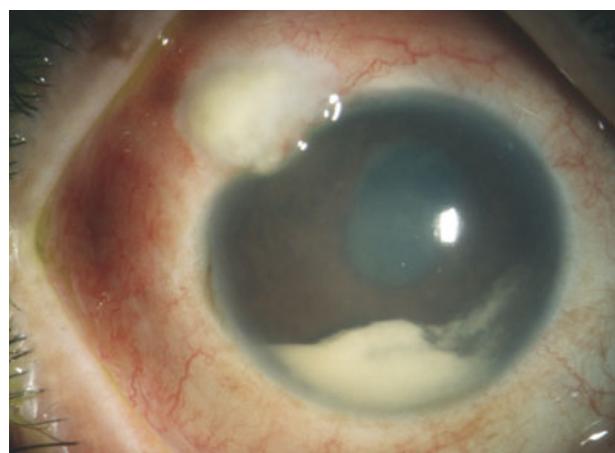
Late bleb infections may occur in at least 1% of eyes with successful filtering operations, and are more common with thin, avascular blebs.⁴⁷ Blebitis is recognized by marked conjunctival injection surrounding a thin, sometimes leaking bleb (Fig. 43-7A). The bleb itself contains a cellular reaction that ranges from layered cells to a chalk white appearance. Other signs and symptoms include blurred vision, mucoid discharge, and pain. Unless treated promptly with fortified antibiotics, endophthalmitis may result (Fig. 43-7B), with potential loss of the eye.⁴⁸ Endophthalmitis is best managed in conjunction with a vitreoretinal surgeon because vitrectomy and intraocular antibiotic injection may be indicated. Patients with filtration blebs should be warned of this complication and always told to seek care immediately if any symptoms of bleb infection develop.⁴⁹

Hypotony and Hypotony Maculopathy

Chronic hypotony may result from many conditions, including overfiltration, bleb leak, choroidal detachment, chronic iridocyclitis, a cyclodialysis cleft, retinal detachment, and severe ocular ischemia. Although most eyes with chronic hypotony maintain good visual function, some develop hypotony maculopathy with significant loss of vision (Chapter 46).

Dysmorphic Blebs

In some eyes, the bleb may become very elevated and diffuse enough to surround the entire limbus. Such blebs may cause chronic discomfort, whereas highly elevated,



B

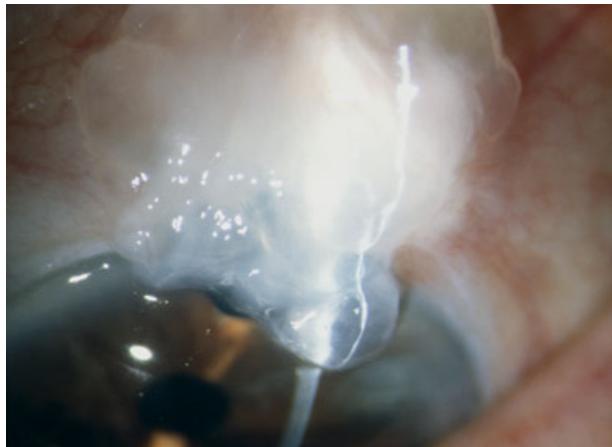
**A****B**

FIGURE 43-8A (A) Uncomfortable blebs typically result from focal elevation at the limbus, often associated with a corneal dellen, or less often, from (B) gradual enlargement of the bleb over the peripheral cornea.

localized blebs may produce corneal dellen and a chronic foreign body sensation (Fig. 43-8A). These are more likely with superonasal filters. Some patients report pain with blinking, due to entrapment of a bubble of air, which then breaks. Other blebs overhang the cornea, occasionally becoming extremely large (Fig. 43-8B).

Treatment of dysmorphic blebs includes frequent artificial tears and emollients, compression sutures, autologous blood injection, and focal application of trichloroacetic acid. When these measures fail, surgical reduction is necessary, with excision of scar tissue and reattachment of the conjunctiva to the limbus.

Central Vision Loss

Permanent loss of central vision following uncomplicated filtration surgery, or "snuff-out," is much more frequent in eyes with advanced visual field loss that extends to fixation ("split fixation").^{50,51} Although the etiology remains unclear, suggested factors include poorly understood effects of rapid ocular decompression and toxic optic nerve damage from retrobulbar anesthesia. Inclusion of epinephrine in retrobulbar anesthesia could theoretically induce vasoconstriction and is generally not recommended or necessary. Although this serious complication is less common with modern surgical techniques, its potential must be discussed prior to filtering surgery with patients who have advanced glaucomatous optic neuropathy.

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CATARACT SURGERY AND GLAUCOMA

Kuldev Singh, M.D., Rommel Bautista, M.D.,
and Weldon W. Haw, M.D.

The prevalence of glaucoma and cataracts increases with each decade of life. Glaucoma occurs in 15% of persons over age 80,¹ and cataracts occur in 70% of people over age 75.² With such a strong dependence on age, it is not surprising that the two conditions frequently coexist in the same eye. Faced with this situation, the surgeon can simply remove the cataract, perform filtration surgery alone, and then do cataract surgery at a later date, or perform a combined filtration and cataract surgery at the same time. The decision of which course to follow depends on the balance between the state of the patient's glaucoma and the visual disability from the cataract. Refinements in small-incision cataract techniques and antimetabolite protocols have increased the popularity of

combined surgery in recent years. However, these techniques present their own challenges and complications, with which the surgeon must remain familiar.

PREOPERATIVE CONSIDERATIONS

CHOICE OF APPROACH

The surgeon can manage the patient with both cataract and glaucoma in three ways: (1) cataract surgery without glaucoma surgery; (2) glaucoma filtration surgery alone, followed by subsequent cataract surgery; or (3) combined, simultaneous cataract and glaucoma surgery (Table 44-1). The decision of which course to follow depends on the

TABLE 44-1 THREE APPROACHES TO CATARACT SURGERY IN THE GLAUCOMA PATIENT

<i>Cataract Surgery Alone</i>	<i>Filtration Surgery With Subsequent Cataract Extraction</i>	<i>Combined Filtration and Cataract Extraction</i>
Indications		
Visually significant cataract Minimal, controlled glaucoma	Severe, uncontrolled glaucoma Multiple risk factors for filtration failure	Significant cataract Uncontrolled glaucoma Mild to moderate glaucoma Intolerable med side effects Optic nerve unable to tolerate Postoperative IOP spike Borderline glaucoma in a patient Unable to tolerate two surgeries Poor medication compliance
Considerations		
Technically simple Rapid postoperative visual recovery Possibility of IOP spike Possible associated reduction in IOP	Requires two surgeries Possible complications from two surgeries Longer cumulative recovery period Possibility of bleb failure after cataract surgery	Technically more complex Single surgery Possibly more complications More frequent postoperative visits Protection against IOP spike Possible IOP lowering Not as effective as trabeculectomy alone

severity of the cataract and the glaucoma. This includes understanding the patient's subjective visual impairment, visual needs and expectations, and the expected visual outcome, as well as the appearance of the optic nerve and visual field deficits, the anticipated target pressure, and the degree of preoperative intraocular pressure (IOP) control.

The surgeon should always choose an approach that will restore the patient's vision, yet minimize the risk of permanent loss of vision from optic nerve damage. The patient should understand that filtration surgery is not performed to improve vision, but rather to preserve visual potential. If a combined procedure is contemplated, the patient should also understand the natural course of visual rehabilitation and the rigorous follow-up required in the postoperative period.

Cataract Extraction Without Glaucoma Surgery

Improvements in surgical techniques, phacoemulsification instrumentation, and intraocular lenses have made cataract extraction and posterior chamber intraocular lens (IOL) implantation safe and effective. Cataract extraction alone is now often the best operation for patients with a visually significant cataract and mild glaucoma, with minimal, if any, field defects and an acceptable IOP using well-tolerated, low-dose medical therapy.

The advantages of this approach over a combined procedure are that it is technically simpler, offers more rapid return of vision, and is associated with fewer complications. In addition, experience has shown that IOP control may improve following cataract surgery using early techniques,^{3–5} as well as modern phacoemulsification.^{6,7} In some instances, preoperative laser trabeculoplasty can help control IOP following cataract surgery.⁸

On the other hand, retained viscoelastic or debris may lead to severe, acute IOP spikes shortly after surgery that may be more common in the glaucoma patient, due to an already compromised aqueous outflow.⁹ These elevations in IOP can reach precarious levels that may irreversibly damage the optic nerve, particularly if it is already extensively damaged. Because of this, glaucoma patients should have their IOP under optimum control prior to undergoing cataract surgery alone.

PITFALL... Intraocular pressure spikes following cataract surgery may produce further optic nerve damage in glaucoma patients.

Glaucoma Filtration Surgery With Subsequent Cataract Extraction (Two-Stage Procedure)

In eyes with severely advanced glaucoma, preventing permanent optic nerve damage takes precedence over the reversible visual disability caused by a cataract. Thus, an eye with a cataract but poorly controlled, advanced glaucoma

on maximal medication is best managed by filtering surgery prior to cataract extraction. This maximizes the likelihood of postoperative IOP control, which is particularly important in patients with multiple risk factors for filtration failure.¹⁰ A trabeculectomy alone will often provide better IOP control than a combined procedure.¹¹ For patients on miotics, successful filtration surgery alone may allow them to discontinue the medication entirely and avoid cataract surgery, due to subsequent enlargement of the pupil. Following a trabeculectomy, subsequent cataract surgery is best done through a temporal clear cornea incision. This minimizes the chance of disturbing the bleb.

All of these advantages must be balanced against the inherent risks of undergoing two consecutive procedures. These include discomfort, anesthetic risks, a longer postoperative recovery, and the potential of accelerating cataract development. In addition, even an apparently uncomplicated clear corneal cataract extraction can result in bleb failure.¹² Some investigators question the effectiveness of long-term IOP control following the two-staged procedure.¹³

Combined Cataract Extraction and Glaucoma Surgery

Combined cataract and glaucoma surgery should be considered in eyes with a visually significant cataract and one of the following: intolerable medication-induced side effects; uncontrolled glaucoma; advanced glaucomatous damage with a high risk of progression; or glaucoma in a patient where two operations or long-term medication use are not feasible.

Early attempts at combined surgery included intracapsular and, later, extracapsular, cataract extraction with filtration surgery.^{14–19} Although some of these reports suggested poor long-term IOP control, there is evidence that combined procedures using phacoemulsification are more successful.²⁰ Indeed, several studies have reported a similar efficacy between combined procedures and isolated filtration surgery.^{21,22} At the least, IOP following combined phacotrabeculectomy is comparable to that of a two-stage surgery and provides earlier visual rehabilitation.²³

The improved success of combined surgery utilizing phacoemulsification likely stems from the smaller incision size, decreased conjunctival trauma, and fewer overall complications, such as hyphema, fibrinous iritis, choroidal detachment, hypotony, and posterior capsular opacification.^{24,25} Other advantages include less astigmatism and accelerated visual rehabilitation.

Although many surgeons perform combined procedures through a single site, others employ a two-site approach, with temporal clear cornea phacoemulsification and separate incision trabeculectomy.^{26,27} So far, both approaches appear to provide comparable IOP control, astigmatic change, and complications.²⁸

The primary advantage of a combined procedure is it allows the patient to avoid the recovery period and complication profile of two separate operations. It may also protect the compromised optic nerve from acute elevations in the IOP during the immediate postoperative period.²⁹

However, these advantages must be weighed against the greater technical challenge of combined procedures, and the risk of early postoperative complications, which include persistent inflammation, hypotony, shallow anterior chamber, and hyphema.³⁰

PREOPERATIVE ASSESSMENT

A complete ocular history and examination should precede any surgical procedure, and will allow the surgeon to decide which of the above approaches is appropriate for the patient. In addition to providing information about the cornea, anterior chamber, and lens, slit-lamp biomicroscopy may reveal a potential for intraoperative vitreous loss. For example, a deep anterior chamber and phakodonesis, or the presence of pseudoexfoliation, may alert the surgeon to weak zonules. The latter condition is also associated with poor pupil dilation. Gonioscopy can help identify patients at risk for angle closure and the rare complication of malignant glaucoma.

Goldmann tonometry, funduscopy, and perimetry will usually determine the state of the patient's glaucoma. In addition, a dilated examination is essential for identifying any underlying macular and peripheral retinal pathology. A Potential Acuity Meter test (PAM) may help anticipate the visual potential following cataract surgery, particularly when combined with perifoveal thresholds derived from automated perimetry in patients with visual acuity better than 20/60.^{31,32} Poor preoperative dilation will also alert the physician to the potential need for small-pupil cataract extraction techniques. The dilated examination should precede surgery by at least 2 days to minimize fatigue to the dilating mechanism.

All topical medications that increase hyperemia should be discontinued prior to surgery. Strong miotics, such as echothiophate iodide, also limit pupillary dilation and may predispose to postoperative bleeding. They should be discontinued at least 2 weeks before surgery. The pupillary effects of pilocarpine and carbachol will generally wear off after 1 day. Other glaucoma medications, including oral carbonic anhydrase inhibitors, may be continued in eyes at high risk for glaucomatous progression.

CATARACT EXTRACTION WITHOUT GLAUCOMA SURGERY

ANESTHESIA

Anesthesia is similar to that described for filtering surgery. However, some surgeons are increasingly inclined to perform cataract extraction alone, or even when combined with

filtration surgery, under topical anesthesia, supplemented with subconjunctival anesthetic.³³ Surgeons should choose the anesthetic with which they feel most comfortable.

SURGICAL TECHNIQUE

Cataract extraction in patients with glaucoma can generally be performed by standard techniques, a detailed description of which is beyond the scope of this chapter. However, specific concerns unique to these patients must be considered. Because the possibility of filtration surgery in the future should never be excluded, the surgeon must always avoid unnecessary manipulation of the conjunctiva. Surgeons using a scleral tunnel approach should move the incision temporally and keep it as small as possible. The recent popularity of a temporal clear cornea approach combined with the insertion of a foldable lens provides a good alternative that minimizes conjunctival manipulation.

PEARL... Temporal clear cornea approach for cataract extraction may avoid unnecessary conjunctival manipulation and increase the success of subsequent filtration surgery, should this be necessary.

The most common intraoperative problems presented by the glaucoma patient undergoing cataract surgery result from poor pupillary dilation and posterior synechiae, which will be discussed in detail below. Additional difficulties, such as loose zonules in patients with pseudoexfoliation, or narrow, crowded anterior segments, require a heightened awareness of potential problems, an unhurried surgical technique, and the ability to react rapidly to any circumstances that seem out of the ordinary. Careful irrigation and aspiration to remove excess viscoelastic, and, occasionally, intracameral injection of carbachol (Miostat), are necessary to reduce the probability of acute postoperative IOP elevations.

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Complications of cataract surgery alone are similar to such surgery in patients without glaucoma, and prophylactic antibiotics and topical steroids are commonly employed. In addition, many surgeons will prescribe prophylactic aqueous humor suppressants to prevent postoperative pressure spikes. Fortunately, patients chosen for this approach are generally well controlled on medical therapy and are not likely to develop severe pressure spikes. If such elevations do occur, they can be managed conservatively and the pressure will usually normalize within a day or two. Because these patients have minimal glaucomatous damage, their optic nerves are relatively resistant to fluctuations in IOP.

COMBINED CATARACT AND GLAUCOMA SURGERY

SINGLE-SITE TECHNIQUE

Combined surgery has evolved from cataract extraction in conjunction with full-thickness filtration procedures or cyclodialysis to more conservative filtration techniques involving a partial-thickness scleral flap. With the increased success and safety of phacoemulsification and IOL implantation,^{34–36} many surgeons have now made the transition to combined surgery using phacoemulsification, the basic steps of which are summarized in Table 44–2.

For a limbus-based conjunctival flap, a corneal bridle suture provides excellent exposure for wound closure and avoids the conjunctival trauma and hemorrhage occasionally seen with a superior rectus muscle suture. A bridle suture is rarely needed for a fornix-based conjunctival approach.

The choice of limbus-based versus fornix-based conjunctival flap depends on surgeon preference. Several studies suggest that the safety and effectiveness of limbus- and fornix-based conjunctival flaps in combined procedures using phacoemulsification are quite similar, even with the use of mitomycin-C.^{37,38} The techniques for

both approaches are similar to that described for a trabeculectomy alone, in Chapter 43.

As with a trabeculectomy, a partial-thickness scleral flap of any shape can be used, depending upon surgeon preference. In general, the flap should measure approximately 3.5 mm horizontally and 2.5 mm vertically and be dissected anteriorly just into clear cornea. A longer incision (6.0 mm) may increase the complication rate, but does not significantly alter final visual acuity or IOP control.³⁹ Many surgeons will simply create an initial cataract tunnel (Fig. 44–1A) and then fashion the flap after IOL implantation.

If used, intraoperative 5-fluorouracil or mitomycin-C are applied in the same way as for a trabeculectomy, tailoring the concentration and duration of application to the individual patient. This is followed by irrigation of the tissues with balanced salt solution (BSS) and removal of all instruments contaminated with mitomycin-C.

In combined surgery, the paracentesis serves several essential functions. It allows injection of viscoelastics, the insertion of a second instrument during cataract extraction, and reformation of the anterior chamber and inflation of the bleb to test for leakage at the conclusion of the operation. The paracentesis is located as needed for second instrument manipulation during phacoemulsification.

TABLE 44-2 SUMMARY OF SINGLE-SITE COMBINED PHACOEMULSIFICATION-INTRAOCULAR LENS-TRABECULECTOMY TECHNIQUE

Step	Instruments
1. Clear cornea bridle suture	8-0 Vicryl or silk, Q-tips to stabilize eye
2. Hemostasis	Diathermy
3. Scleral flap	69 Beaver blade, fine forceps
4. Antimetabolite	MMC (0.2–0.5 mg/mL) or 5-FU (50 mg/mL), sponge
5. Antimetabolite irrigation	Balanced salt solution
6. Limbal paracentesis	SuperSharp or Beaver 75 blade
7. Viscoelastic injection	Healon, viscoat, or similar viscoelastic
8. Anterior chamber entry	3.0 or 3.2 mm keratome
9. Capsulotomy and hydrodissection	Bent capsulotomy needle, Utrata forceps, BSS on 27 g cannula
10. Phacoemulsification	Phacoemulsifier
11. IOL insertion	IOL, insertion or folding forceps
12. Viscoelastic removal	Irrigation and aspiration unit
13. Miochol injection	
14. Sclerectomy	Kelly-Descemet's punch, fine forceps, instrument wipe
15. Peripheral iridectomy	Fine forceps, Vannas scissors
16. Secure scleral flap	10-0 nylon suture, 0.12 or Pierce-Hoskins forceps
17. Closure of conjunctival flap	10-0 nylon on noncutting needle, nontoothed forceps
18. Reinflate bleb	Balanced salt solution
19. Siedel test	Fluorescein strip
20. Subconjunctival injection	Cefazolin 50 mg/0.5 mL, dexamethasone 2.0 mg/0.5 mL
21. Antibiotic ointment	Polysporin or erythromycin ointment
22. Patch, shield	

IOL, intraocular lens; MMC, mitomycin-C; 5-Fu, 5-fluorouracil.

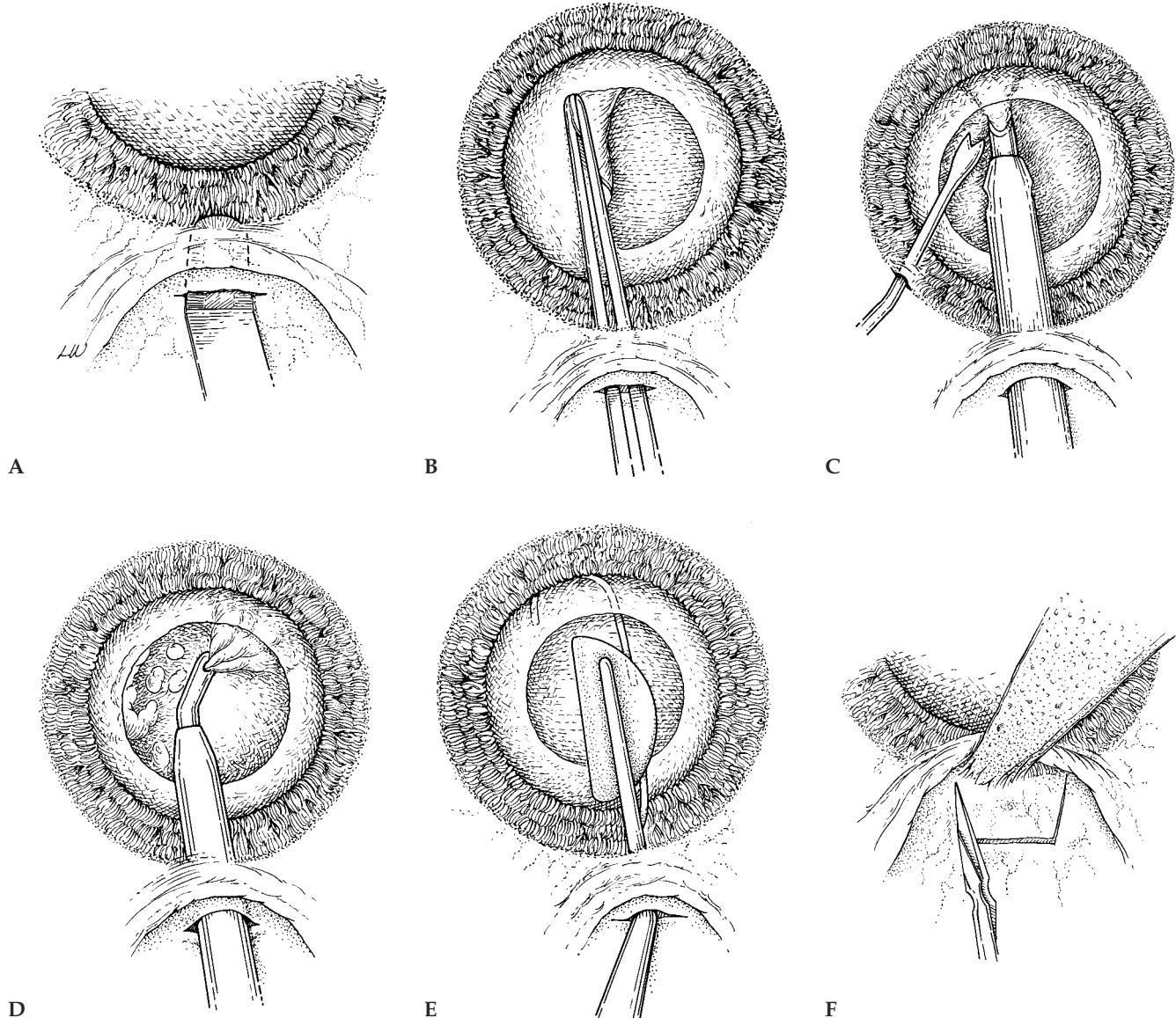


FIGURE 44-1 Major steps of a single-site phacoemulsification combined with trabeculectomy. (A) Following the conjunctival flap, a typical cataract tunnel is created, beginning just above the limbus. Antimetabolites may be applied at this point, prior to paracentesis. (B) A continuous tear capsulotomy is followed by (C) standard phacoemulsification and (D) cortical aspiration. A two-handed phacoemulsification technique is especially useful when dealing with a small pupil. (E) Foldable lens implantation allows the surgeon to minimize the wound size and simplifies the creation of the trabeculectomy flap and fistula. (F) The cataract tunnel is easily converted into a trabeculectomy flap by incising the edges of the tunnel up to the limbus with fine scissors or a sharp blade. Fistula creation with a Kelly Descemet's punch, peripheral iridectomy, and closure of the scleral and conjunctival flaps are performed as described for standard trabeculectomy (Fig. 43-1E).

After injection of viscoelastic, a 3.0 mm keratome, or similar instrument, is used to enter the anterior chamber through the anterior aspect of the scleral tunnel. Pupillary enlargement techniques, discussed in the following text, are performed as needed.

A continuous tear capsulotomy is performed using a bent capsulotomy needle or Utrata forceps (Fig. 44-1B). Complete hydrodissection and hydrodelineation with BSS are essential to completely mobilize the nucleus and epinucleus. This minimizes traction on zonules during

phacoemulsification, and is particularly important in eyes with trauma or pseudoexfoliation.

Removal of the nucleus by phacoemulsification and cortical clean-up using a standard automated irrigation and aspiration system is performed in standard fashion (Fig. 44-1C,D). Following injection of additional viscoelastic to inflate the capsular bag, the scleral tunnel incision is enlarged as needed, and a foldable posterior chamber intraocular lens, or PMMA nonfoldable lens, is inserted into the capsular bag (Fig. 44-1E). Following

aspiration of viscoelastic, Miostat is injected into the anterior chamber to facilitate making a peripheral iridectomy.

A scleral tunnel incision can be easily converted to a trabeculectomy flap by incising the anterior flap at either end up to the limbus, using either a 75 Beaver blade or fine-tipped Vannas scissors (Fig. 44-1F). The Kelly Descemet's punch is used to excise a block of corneoscleral tissue, as described for a trabeculectomy, using an instrument wipe or methylcellulose sponge to clean tissue from the punch between each bite (Fig. 43-1E).

The iridectomy is performed as described for a trabeculectomy. After this, the fistula must be completely patent, without retained cortical debris, iris pigment, lens capsule, or vitreous incarceration. The iridectomy should be sufficiently large and all bleeding stopped before closing the scleral flap.

Closure of the scleral flap and conjunctiva is performed as described for a trabeculectomy. Injection of BSS through the limbal paracentesis should elevate the bleb and allow the surgeon to inspect the wound for leakage. Any leaks should be closed at the time of surgery with 10-0 nylon or 9-0 Vicryl on a tapered needle.

SEPARATE-SITE TECHNIQUE

A superior trabeculectomy can also be combined with temporal clear cornea phacoemulsification.^{26,27} Following a temporal clear cornea phacoemulsification and IOL placement, the surgeon then moves to the 12 o'clock position to perform a trabeculectomy in the typical fashion.

The theoretical advantages of this approach include reduced manipulation of the conjunctiva and sclera, which may limit postoperative inflammation and enhance long-term success. Without the bleeding, bulky conjunctival and scleral flaps, phacoemulsification may be more easily performed, with improved visibility. In addition, with separate incision sites, flap suture lysis can be isolated from the cataract wound incision.

Cataract extraction combined with endoscopic ciliary process photocoagulation represents a potential alternative to traditional combined procedures. Uram has demonstrated improved visual acuity, a 57% decrease in IOP, and minimal complications with a mean follow-up of 19 months.⁴⁰ Although the safety and long-term efficacy of this approach remain unknown, preliminary results are encouraging.

POSTOPERATIVE MANAGEMENT

Postoperative care after combined surgery is similar to that for trabeculectomy and includes topical, broad-spectrum antibiotics and steroids. It is usually administered approximately every 4 hours but may be given more or less frequently. The steroid drops should be gradually tapered according to the clinical status over 3 to 4 months. Rapid tapering is a common cause of

delayed trabeculectomy failure, whether or not it is combined with cataract surgery.

Although useful in patients undergoing cataract surgery alone, aqueous suppressants may limit flow through the trabeculectomy fistula and potentially lead to a flat bleb. These medications should be avoided following combined surgery and discontinued in the fellow eye if the bleb is shallow with low IOP and no wound leak. In contrast, a shallow bleb associated with elevated IOP may require further postoperative interventions such as digital massage, laser suture lysis, 5-fluorouracil injections, or bleb needling. All of these procedures are discussed in Chapter 43.

COMPLICATIONS

The potential complications of combined cataract extraction, IOL insertion, and filtration procedures are an accumulation of the complications of each individual procedure. They may arise during surgery, and in the early and late postoperative phases.

Possible intraoperative complications include anesthetic complications, retrobulbar hemorrhage, conjunctival "buttonholes," bleb leaks, Descemet's detachment, hyphema, shallow anterior chamber, choroidal hemorrhage, and vitreous loss. Early postoperative complications include hypotony or IOP elevation, conjunctival defect, excessive filtration, choroidal detachment, uveitis, hyphema, dellen formation, and central vision loss. Filtration failure, leaking filtration bleb, blebitis and endophthalmitis, spontaneous hyphema, hypotony, posterior subcapsular opacification, ciliochoroidal detachment, staphyloma, ptosis, and sympathetic ophthalmia can all occur in the late postoperative period.

Patients undergoing combined procedures may have a slightly higher risk of early postoperative complications, such as inflammation, hypotony, shallow anterior chamber, and hyphema. Additionally, some have suggested that long-term IOP stability in combined procedures may not be as reliable as with a two-stage intervention.^{26,41}

SPECIAL INTRAOPERATIVE CONSIDERATIONS

Glaucoma patients undergoing cataract surgery present unique surgical challenges. The cataract surgeon performing such surgery should be familiar with the various maneuvers necessary to deal with a small pupil, pseudoexfoliation, and the use of antimetabolites.

ENLARGING A MIOTIC PUPIL

A miotic, immobile pupil may result from chronic miotic therapy, posterior synechiae, pseudoexfoliation syndrome, or simple senile miosis due to sclerosis of the iris

stroma and blood vessels in conjunction with dilator muscle atrophy.⁴² Although in the past as many as 42.5% of patients with glaucoma required sphincterotomies during cataract extraction,⁴³ this has become less common as our selection of nonmiotic glaucoma medications expands. However, miosis remains a significant problem. The limited visibility afforded by a small pupil interferes with both capsulorrhexis and phacoemulsification of the lens nucleus, increasing the chance of capsule rupture and vitreous loss.

The surgeon should always first try to enlarge a miotic pupil by injecting a viscoelastic agent in the center of the pupil. Healon GV (Pharmacia-Upjohn, New Jersey), a high-molecular-weight, viscous type of hyaluronic acid, is an excellent choice. Viscoelastic injection, in conjunction with mechanical sweeping with the cannula, can also be used to break posterior synechiae. Occasionally, a superior peripheral iridectomy followed by injection of the viscoelastic into the posterior chamber will help to lyse superior and inferior synechiae.

If the pupil is still too small, instruments like the Graether collar button or Kuglan hooks can be used to mechanically enlarge it by stretching the sphincter or by creating many small sphincter tears. Stretching the pupillary margin in the horizontal and vertical meridia will sufficiently enlarge the majority of senile miotic pupils (Fig. 44-2A).

PEARL... Stretching the pupillary margin in the horizontal and vertical meridia will sufficiently enlarge the majority of senile miotic pupils.

Iris retractors are useful if these methods fail. Monofilament nylon retractors, such as those designed by DeJuan,⁴⁴ can be placed with four limbal corneal incisions made 90 degrees apart, oriented posteriorly toward the pupillary margin. Each hook engages the pupil and is drawn toward the periphery by sliding the Silastic sleeve

down the shaft to enlarge the pupil. To remove the retractors, the surgeon slides the Silastic sleeve toward the center of the pupil, disengages the iris, and pulls the retractor out through the paracentesis.

Surgical maneuvers to enlarge the pupil for phacoemulsification include creating multiple partial-thickness sphincterotomies at the pupillary margin, as described by Fine.⁴⁵ This technique, which can be supplemented with additional viscoelastics and mechanical iris stretching, leaves the iris sphincter largely intact, preserving its ability to respond to typical pharmacological agents (Fig. 44-2B). Occasionally, a sector iridectomy created by extending a superior iridectomy into the pupillary aperture is necessary for extracapsular cataract extraction. After removing the cataract and placing the IOL, the surgeon should always reposition and constrict the iris, both mechanically and pharmacologically.

SMALL PUPIL PHACOEMULSIFICATION

Small pupil phacoemulsification relies on an adequate, continuous tear capsulotomy and careful fracture and removal of the nucleus through the pupil in pieces. By making the initial tear more centrally, the surgeon can often safely extend the tear to the pupillary margin, or beyond, by using additional viscoelastic or a Kuglan hook to visualize the edge of the capsulotomy. Following hydrodissection and hydrodelineation, the nucleus and epinucleus should be completely mobile. This greatly decreases the chance of capsule tear during phacoemulsification.

Fracturing the nucleus into multiple segments and then emulsifying each one in the pupillary axis is tedious, but effective.⁴⁶ Because a small pupil limits the view of the peripheral nucleus, the grooves tend to be deep, but short. A methodical approach, using frequent rotation of the nucleus and extension of the grooves, often bringing the inferior nucleus into view with a second instrument via the paracentesis, will typically allow the surgeon to create four nuclear quarters. After separating the quarters

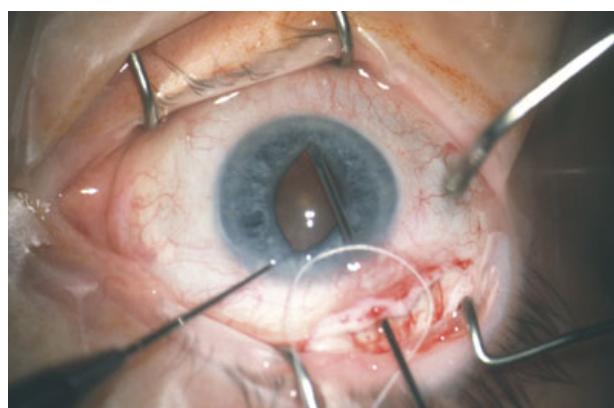
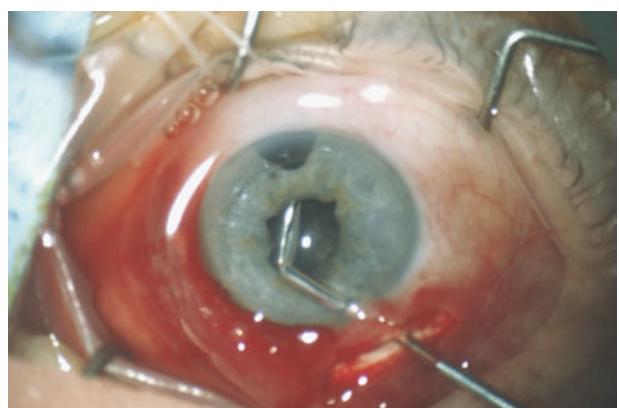


FIGURE 44-2 (A) A stubborn, miotic pupil can often be enlarged with bimanual stretching of the pupillary border or, if necessary, (B) partial sphincterotomies with intraocular scissors.



B

using the second instrument and phaco tip, each individual quarter is engaged with the tip and drawn into the midpupil along the iris plane for safe phacoemulsification.⁴⁷ Reducing the flow and vacuum settings during phacoemulsification helps the surgeon minimize inadvertent iris chafing and damage.

PSEUDOEXFOLIATION SYNDROME

Patients with pseudoexfoliation appear to have a weak zonule apparatus, and nearly 47% dilate poorly.⁴⁸ For these reasons, cataract surgery in these patients carries a higher risk of zonule dialysis, capsular rupture, phacodonesis, lens decentration, and vitreous loss.^{49–51} The surgeon's best defense against these problems lies in recognizing their potential before surgery, and adopting a careful, methodical approach, in addition to the small pupil techniques discussed above. Postoperative inflammation, which is often greater in these patients due to alterations in the blood–aqueous barrier, may be reduced by fastidious cortical removal, minimizing iris manipulation, and using surface modified IOLs and aggressive postoperative steroids.^{52,53}

ANTIMETABOLITES

As with trabeculectomy alone, bleb failure in combined surgery most commonly results from fibrosis in the subconjunctival/sub-Tenon's space, or episclera. With the refinement of adjunctive antimetabolite protocols, many glaucoma surgeons now use these agents to increase IOP control following combined surgery.^{54–57} While there are currently few well-controlled studies evaluating risk factors for failed filtration in combined procedures,⁵⁸ these factors are not significantly different from those in filtration surgery alone.

When using antimetabolites in combined procedures, the surgeon can minimize their well-known side effects through meticulous surgical technique and attention to detail. This includes adequately suturing the scleral flap to avoid overfiltration and hypotony, handling all tissues carefully and gently to prevent conjunctival "button-holes" and careful closure of the conjunctiva. Finally, the concentration and duration of antimetabolite application should be titrated to the risk factors of the individual patient, using the lowest concentration and shortest exposure time needed to achieve the target IOP.

Mitomycin-C

In combined procedures, protocols using mitomycin-C (MMC) do not differ significantly from those in trabeculectomy alone. Various authors have reported on the efficacy of MMC in combined procedures involving both ECCE⁵⁵ and phacoemulsification.^{56,59–64} Although one large clinical trial did not support the use of MMC in all

combined procedures,⁵⁷ the results still suggested that it may still benefit patients at higher risk of filtration failure.⁵⁸

As with filtering surgery alone, the use of MMC in combined procedures must be balanced against its potential complications. These include wound leaks, superficial punctate keratitis, persistent hypotony, endothelial toxicity, and wound instability.^{55,61}

5-Fluorouracil

Overall, 5-fluorouracil (5-FU) in combined procedures may be less effective than adjunctive MMC. Although postoperative 5-FU subconjunctival injections in combined surgery have been reported to improve the 1-year success rate of IOP control,^{65,66} this is not supported by other large, prospective clinical trials.⁶⁷

5-FU may be administered intraoperatively or postoperatively. Intraoperative 5-FU appears to have a lower complication rate than MMC. However, because it may be less potent than MMC, subconjunctival postoperative injections may still be necessary,^{68–71} titrating the dosage to the individual patient and appearance of the bleb. This approach requires more patient cooperation and increases the risk of corneal complications.

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AQUEOUS SHUNTS

Paul A. Sidoti, M.D.

Glaucoma drainage implants, or aqueous shunts, are useful for managing complicated glaucoma, particularly when trabeculectomy has failed to control the intraocular pressure (IOP) or is unlikely to succeed. All of these devices rely on the same principle. A silicone tube shunts aqueous humor from the anterior chamber or vitreous cavity to an extraocular fluid reservoir produced by a fibrous capsule that forms around a synthetic plate or band sutured to the equator of the eye.

Over the years, surgeons have devised many modifications in the basic design of these implants to improve their effectiveness and reduce complications. These primarily involve varying the size and shape of the plate, or explant, and incorporating a valve or flow restriction device. For nonvalved shunts, several surgical techniques now exist to lower the IOP and yet avoid profound hypotony during the early postoperative period.

In spite of these advances, IOP remains relatively unpredictable immediately after surgery and many patients will still require chronic glaucoma medications to achieve successful pressure control. In addition, these patients require long-term surveillance to detect and manage potential complications, such as tube and plate erosion and chronic strabismus. Successful aqueous shunt surgery requires judicious implant and patient selection, exacting surgical technique, and a thorough understanding of how to manage their short- and long-term postoperative complications.

BACKGROUND

The benchmark glaucoma drainage implant was developed^{1,2} and later modified^{3–5} by Molteno in the early 1970s. Several newer devices have since been introduced with modifications designed to enhance IOP control or limit early postoperative complications. All glaucoma

drainage devices consist of a silicone tube with an internal diameter of 0.3 mm connected to a drainage plate or band of synthetic material (the explant) that is attached to the wall of the eye. These devices vary in their surface area, thickness, shape, and composition of the drainage plate. In some, a pressure-sensitive valve is placed at the junction between the tube and drainage plate to regulate fluid flow. Increasing experience with these implants has expanded their use for refractory glaucomas due to a wide variety of ocular conditions.

Surgical implantation involves suturing the drainage plate to the episclera posterior to the level of the rectus muscle insertions and inserting the distal end of the tube into the anterior or posterior segment of the eye. The synthetic drainage plate encourages formation of a fibrous capsule around all sides of the plate over several weeks. This provides a subconjunctival reservoir into which aqueous humor is shunted via the silicone tube. Fluid diffuses through this capsule and is absorbed by the orbital and episcleral vasculature and lymphatics. The resistance of the capsule wall to fluid diffusion, combined with its total surface area, determines the final IOP in a complex fashion.

FACTORS DETERMINING INTRAOCULAR PRESSURE CONTROL BY GLAUCOMA DRAINAGE DEVICES

Early studies in both animals⁶ and humans^{7,8} suggested that these drainage devices reduced IOP in direct proportion to the internal surface area of their fibrous capsule. Using a primate model of glaucoma, Minckler et al confirmed that fluid flow through the capsule around a Molteno implant (Optomat Supplies, Ltd., Dunedin, New Zealand, Starr Surgical Co., Monrovia, CA, IOP, Inc., Costa Mesa, CA) occurs by passive diffusion,⁶ that resistance to this flow determines the final IOP, and that perfusion rates through bleb capsules are directly proportional to

the surface area of the scleral plate. In 1992, Heuer et al⁷ demonstrated that double-plate Molteno implants yielded significantly better success rates and greater mean IOP reduction than the single-plate implant.

However, IOP reduction is not strictly proportional to the surface area of the explant.^{9–11} Two studies comparing the double-plate Molteno and Schocket implants showed that the two devices were similarly effective, despite the nearly twofold greater surface area of the latter.^{10,11} This may be due to the low, tightly adherent capsule of the Schocket implant, as compared with the higher vaulted bleb of the Molteno.^{12,13} Even when similar devices are compared, there does not appear to be a direct relationship between implant surface area and IOP reduction.^{8,14}

SPECIAL CONSIDERATION

Eyes with limited aqueous humor production may develop prolonged hypotony after implant surgery and may do better with a smaller-surface-area drainage device or even a valve. These conditions include uveitis, ocular ischemia, previous cyclodestruction, and fibrovascular ingrowth.

PREOPERATIVE CONSIDERATIONS

CLINICAL INDICATIONS

Most surgeons reserve glaucoma drainage implants for eyes that have failed trabeculectomy despite antimetabolites. Another common indication is the presence of conjunctival injury and scarring, which prevents safe dissection of a conjunctival or scleral flap. However, postoperative pressures in the 8 to 12 mm Hg range are uncommon with aqueous shunts and generally require one or more adjunctive aqueous suppressant medications. Patients with advanced glaucomatous optic nerve damage or low-tension glaucoma might be better served by an antimetabolite filter.

PREOPERATIVE ASSESSMENT

The demographic characteristics of the patient and specific anatomic and clinical features of the eye will often influence the approach to glaucoma implant surgery. Many surgeons prefer using a large-surface-area device in young patients, and smaller-surface-area shunts in elderly patients. Because shunts with valves can be unpredictable, and they do not protect against marked hypotony from mechanical pressure on the globe, these should be avoided in very young children or otherwise uncooperative patients.

Patients predisposed to postoperative inflammation and scarring, such as uveitis or anterior segment neovascularization, may also need a larger-surface-area plate. Because postoperative inflammation, fibrin formation, or intraocular hemorrhage can obstruct the valve, drainage devices with flow-restricting mechanisms should be used with caution in these patients. In general, the target postoperative IOP depends on the severity of glaucomatous optic nerve head damage. Many surgeons feel that patients who require lower IOP should have a larger surface area implant. Although this does not guarantee better pressure control, the surgical risk, expense, technical difficulty, and complications of these devices vary little from those of smaller shunts.^{7,8,10,11,14}

The presence of a crystalline lens makes it difficult to position the tube away from the corneal endothelium. In a pseudophakic eye, the lens optic can protect the tip of the tube from obstruction by iris or vitreous and allow even more posterior insertion in eyes with a large peripheral iridectomy. In aphakic eyes, vitreous should be removed from the anterior chamber and iris plane, and the tube kept away from the pupil and any iridectomies.

Careful preoperative gonioscopy helps the surgeon identify and avoid extensive peripheral anterior synechiae that can prevent deep placement of the tube. This may also influence the selection of the quadrant for drainage plate placement, although the tube itself can be placed as much as 30 to 45 degrees to either side of the drainage plate if necessary.

Extensive subconjunctival scarring following scleral buckling surgery often complicates the placement of a drainage device, and a flexible, low-profile device, such as the Baerveldt implant (Pharmacia and Upjohn Co., Peapack, NJ) may be easier to insert. However, these patients have a higher risk of conjunctival wound dehiscence and epithelial invasion.¹⁵ For patients with severe scarring and wide, encircling silicone tires, some surgeons prefer to place a tube into the preexisting fibrous capsule around the band.^{16,17}

Patients with high hyperopia, unknown refractive error, angle-closure glaucoma, or other features suggestive of small axial length should undergo A-scan echography. This allows timely adjustment of surgical technique and anticipation of complications related to the small size of these eyes.

SELECTION OF A DRAINAGE DEVICE

Several glaucoma drainage devices are commercially available (Fig. 45–1A–F). Table 45–1 presents the characteristics that affect the function and clinical use of each device. The most significant of these are the presence of a flow restriction device, or valve, and the dimensions of the plate.

A shunt must provide effective IOP control yet avoid profound hypotony prior to encapsulation of the scleral plate. To this end, several devices use pressure-sensitive valves, or flow-restricting modifications.^{18–22} The “valves” of the Krupin (Hood Laboratories, Pembroke, MA) and Ahmed (New World Medical, Inc., Rancho Cucamonga, CA) implants theoretically open and close between 8 and 11 mm Hg, whereas the “inherent conductive resistance” of

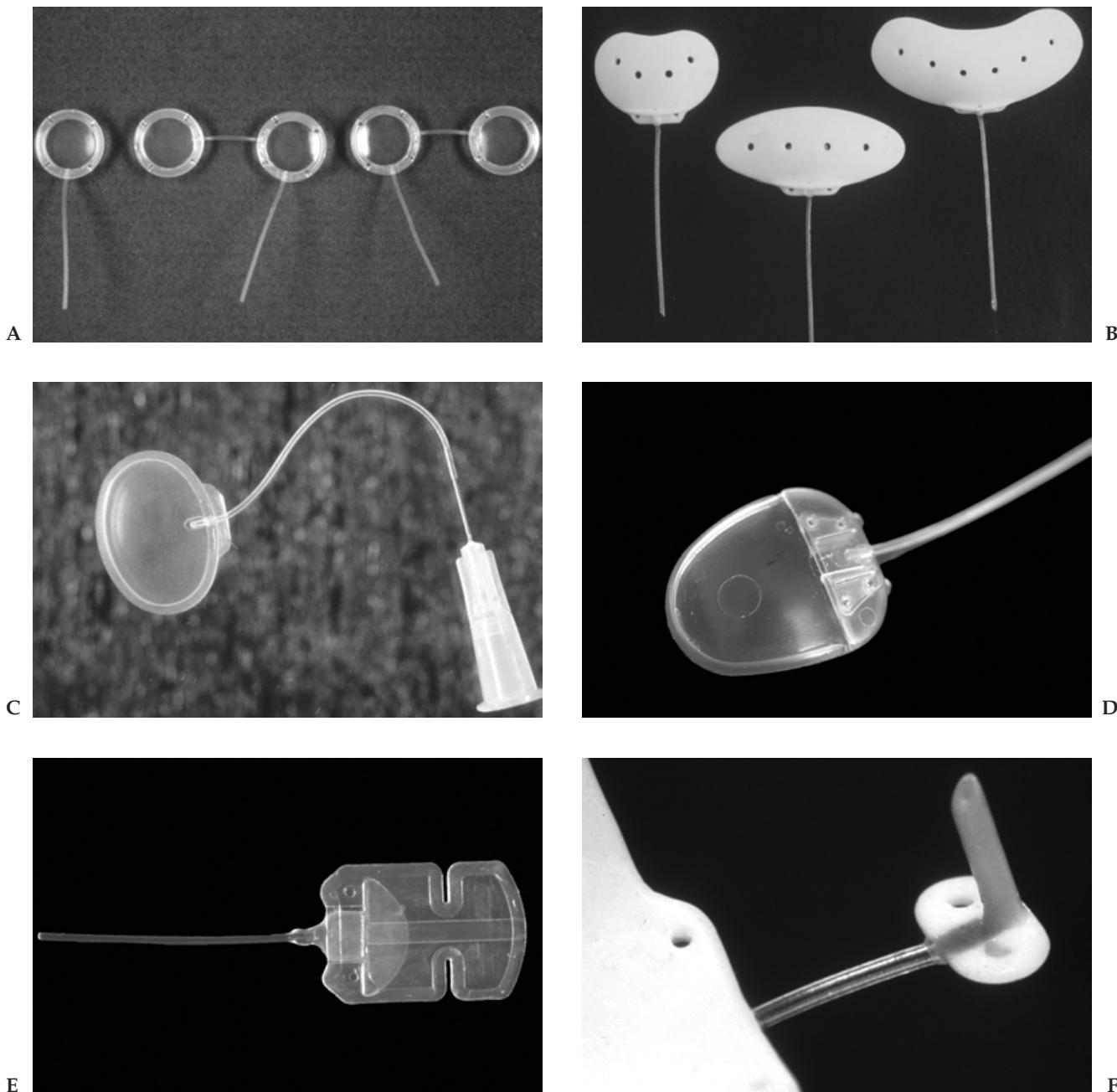


FIGURE 45-1 Commonly used glaucoma drainage implants. (A) Single-plate (left) and double-plate (right) Molteno implants. (B) Baerveldt glaucoma implants, 250 mm² (left), 350 mm² (center), and 425 mm² (right). (C) Krupin eye valve with disk. (D) Single-plate Ahmed glaucoma valve (a double plate is also available). (E) OptiMed glaucoma pressure regulator. (F) The Baerveldt pars plana glaucoma implant with the Hoffman elbow modification.

the OptiMed implant (OptiMed International, Inc., Santa Barbara, CA) is designed to keep IOP between 8 and 19 mm Hg. However, none of these devices entirely eliminates either early postoperative hypotony or marked IOP elevations,^{20,22–30} nor can they keep external pressure on the globe from reducing IOP to below physiological levels.

The primary benefit of these valved devices is their ability to provide immediate IOP reduction, without temporary tube ligatures or stents (Table 45–2). This reduces operating time and eliminates the potential need for a second opera-

tion, although most require “priming” by injecting balanced salt solution through the end of the tube (Fig. 45–4A). A valved drainage implant may also be useful in cases prone to prolonged hypotony, such as eyes with aqueous hyposecretion, and when used with mitomycin-C, which may delay scleral plate encapsulation.^{31–35} However, once the fibrous capsule has formed, the valve mechanism is no longer necessary. It remains a potential site for obstruction of particulate debris, fibrin, blood, or fibrous tissue during the early and late postoperative period.^{36–38}

TABLE 45-1 CHARACTERISTICS OF GLAUCOMA DRAINAGE DEVICES

Device	Surface Area*(mm ²)	Flow Restriction	Plate Material	Plate Thickness (mm)	Diameter (mm) Anteroposterior	Diameter (mm) Circumferential
Molteno Implant		no	polypropylene	2.16	12.8	12.8
Single-plate	129					
Double-plate	257					
Baerveldt implant		no	silicone	0.84		
250	260.5				13.0	22.0
350	343.7				13.0	32.0
425	440.9				13.0	36.0
Krupin eye valve with disk	184	yes	silicone	1.75	13.0	18.0
Ahmed glaucoma valve	184‡	yes	polypropylene	1.90	16.0	13.0
ACTSEB (Schocket)		no	silicone			
#20 band	300†				4.0	variable
#220 band	450†				6.0	variable
OptiMed Glaucoma Pressure Regulator	140	yes	silicone	1.30	14.0	10.0

ACTSEB, anterior chamber tube shunt to encircling band.

*Two-dimensional scleral contact area of band or plate.

†Assuming a diameter of 24 mm at the equator of the globe and a 360 degree encircling band.

‡ Also available as a 2 plate device

TABLE 45-2 COMPARISON OF VALVED VERSUS NONVALVED DEVICES

	Valved	Nonvalved
Advantages	Rapid control of IOP Single-stage procedure Minimize incidence of severe hypotony	Less chance of late occlusion Low incidence of hypotony with tube ligature Option to use larger plate sizes
Disadvantages	Function occasionally unpredictable Late valve obstruction Plate size generally smaller	Two-stage procedure possibly necessary Surgical modifications needed to prevent severe, immediate hypotony (unpredictable) Elevated IOP prior to ligature release

IOP, intraocular pressure.

Nonvalved devices all require some type of surgical modification to avoid early postoperative hypotony and yet provide early IOP control. Most surgeons employ a removable stent or absorbable suture to “ligate” the tube. Methods to provide IOP control while the tube is occluded are discussed in the following text.^{39,40} In spite of these techniques, excessively high and low IOP can still occur.

CONTROVERSY

Valved and nonvalved devices each have their advantages and disadvantages. The choice between the two often depends on physician preference and familiarity with the surgical techniques.

As already discussed, IOP control does not strictly correlate with implant surface area. However, many surgeons prefer a smaller plate in eyes with decreased aqueous production,^{41,42} and will implant a second plate if IOP control remains inadequate. Larger implants are frequently employed in eyes needing lower postoperative IOP.

SURGICAL TECHNIQUE

CONJUNCTIVAL INCISION

Glaucoma drainage devices can be implanted through either a limbus- or fornix-based conjunctival flap. The former provides excellent posterior exposure, decreases the risk of limbal wound leaks and conjunctival retraction, and may preserve limbal stem cells. However, extensive

conjunctival and episcleral scarring can prevent adequate anterior dissection of the flap. In addition, the resulting wound may overlie the plate, increasing the potential for wound dehiscence, postoperative leakage, and epithelial downgrowth.

A fornix-based flap (Fig. 45–2A) provides excellent limbal exposure and greater latitude in choosing the fistula site. A fornix-based conjunctival/Tenon's flap begins with a limbal peritomy, ranging from 90 to 180 degrees, depending on the implant, with radial relaxing incisions at either end. Patients with severe conjunctival scarring require a larger incision to minimize the risk of tearing the inelastic conjunctiva and to facilitate closure.

With either approach, the flap should be as thick as possible, containing both conjunctiva and Tenon's capsule. This allows more secure closure and protects against wound dehiscence and implant exposure.

SCLERAL EXPLANT INSERTION

Most surgeons prefer the superotemporal quadrant for shunt placement. This provides good exposure and avoids the superior oblique tendon. Furthermore, the upper eyelid protects the anterior portion of the tube, the patch graft, and the scleral fistula. When this region is not available, some surgeons prefer the inferotemporal or inferonasal

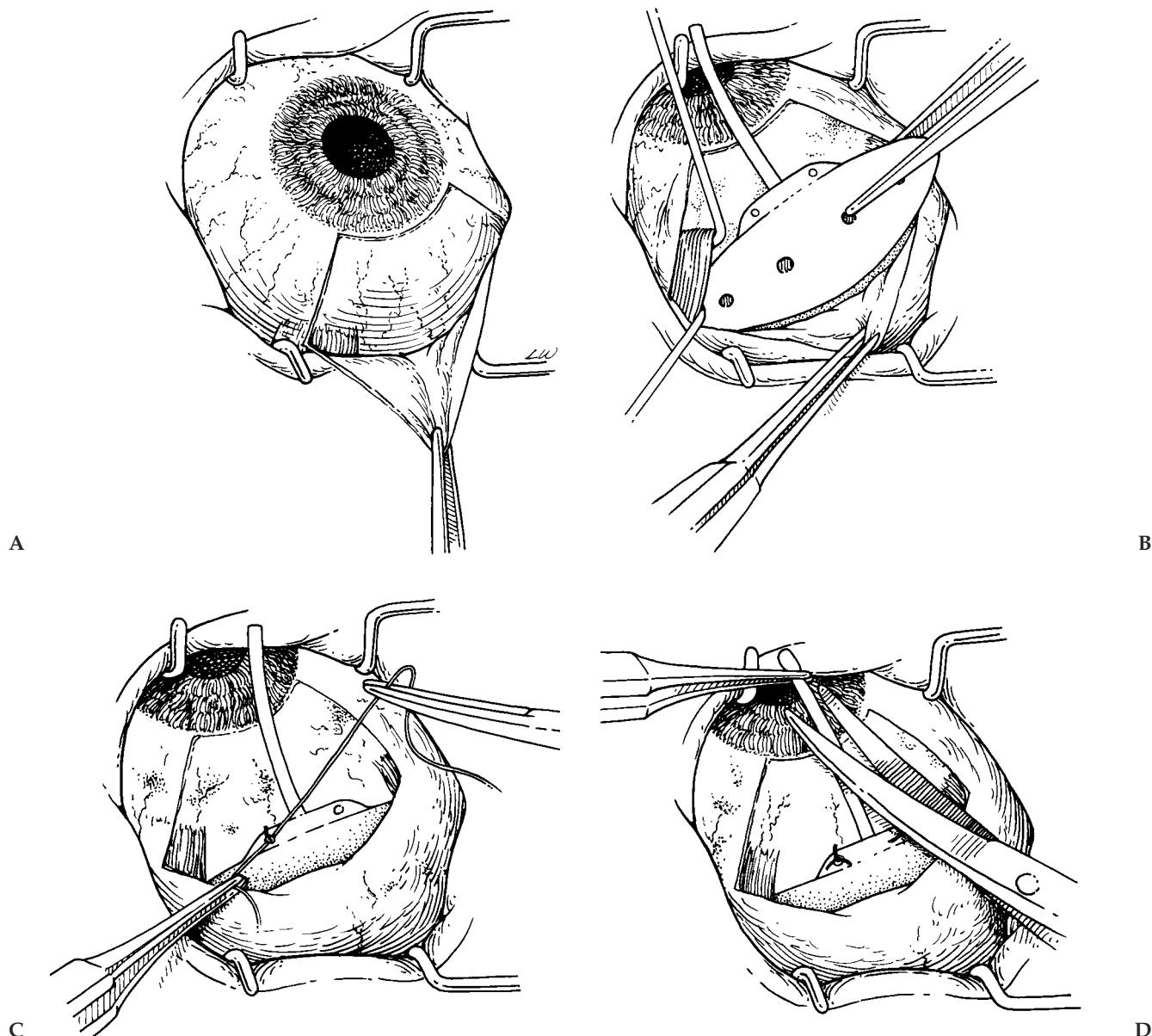


FIGURE 45-2 The major steps of aqueous shunt implantation. (A) Limbal conjunctival incision and peritomy to expose the rectus muscle insertions. (B) Placement of the implant between adjacent rectus muscle insertions. (C) Suturing of the eyelets to the sclera just posterior to the rectus muscle insertions. (D) Cutting the tube 1 to 2 mm anterior to the limbus with an anterior bevel.

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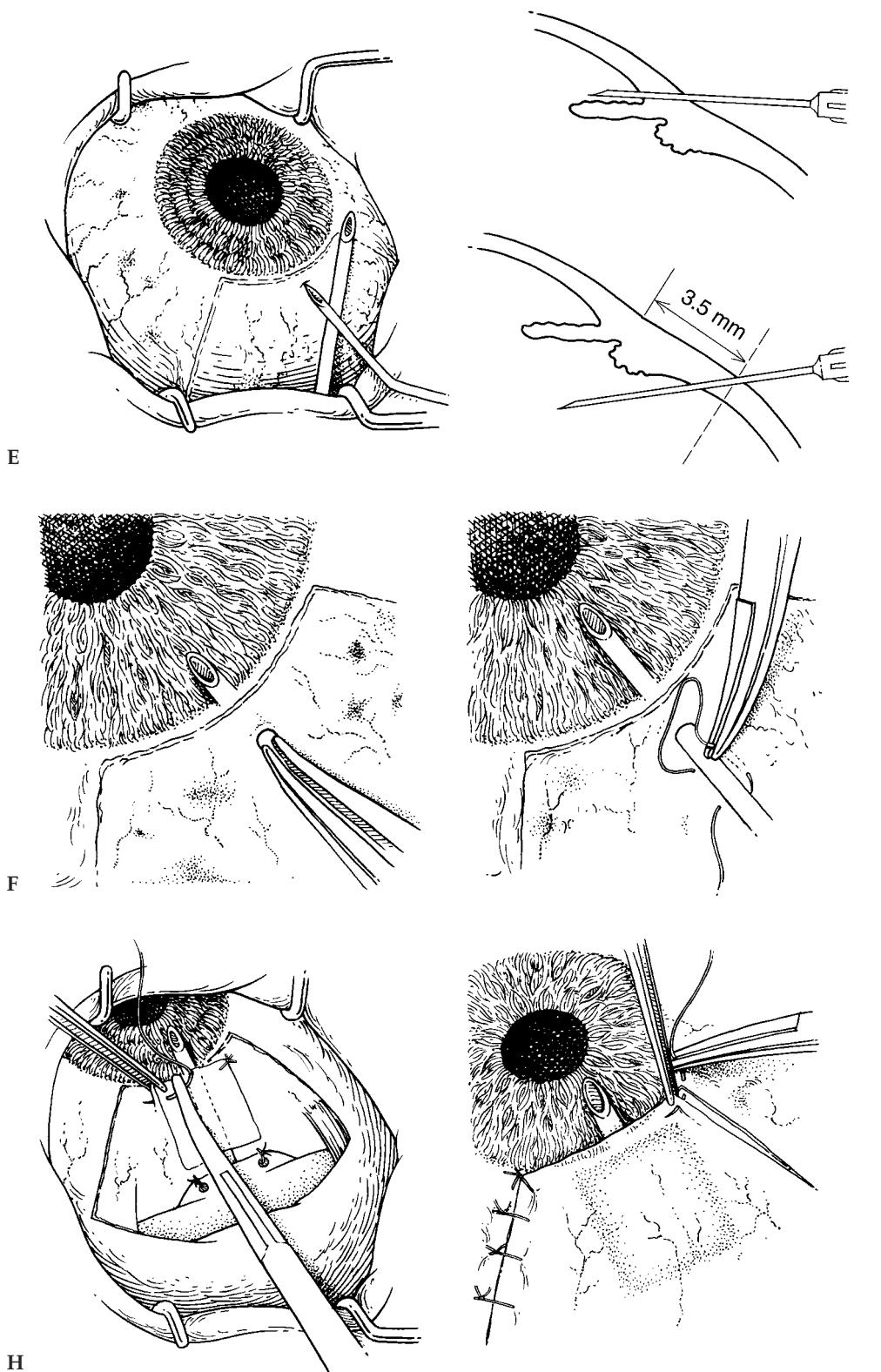


FIGURE 45-2 (E) Site of fistulization with a 23-gauge needle, just posterior to the blue line for a limbal insertion. Top inset shows needle orientation for limbal insertion, parallel to the iris plane. Bottom inset shows orientation for pars plana insertion of a standard tube, angled slightly toward the iris, but not perpendicular to the scleral surface (dashed line). (F) Insertion of tube into fistula using a tubing-introducing forceps. (G) Proper positioning of tube in eye, with the external portion anchored to the episclera using a mattress suture. (H) Placement of patch graft over the limbal fistula and anterior portion of the tube. The anterior edge of the graft lies immediately posterior to the conjunctival incision, and the posterior edge ends just anterior to the plate. (I) Suturing the conjunctiva with absorbable suture at either corner, stretching the conjunctiva over the peripheral cornea, anterior to the patch graft.

quadrant over the superonasal region to avoid the superior oblique. Because the relatively long Ahmed implant can compress the optic nerve when placed on the nasal side of the globe, its anterior edge should be no more than 8 mm posterior to the limbus when placed in this location.

The surgeon must identify the insertions of the two adjacent rectus muscles bordering the quadrant of insertion and, for a Baerveldt implant, place the wings beneath the muscle bellies (Fig. 45–2B). Sliding the implant anteriorly, up to the superior rectus insertion, ensures that it is not caught under the superior oblique tendon. The double-plate Molteno implant can be inserted with the connecting tube either over or under the intervening rectus muscle. It is not necessary to disturb the rectus muscles when implanting the smaller, single-plate Molteno, Krupin, Ahmed, OptiMed, or White implants. Valved devices require “priming” prior to insertion (Fig. 45–4A).

SCLERAL EXPLANT FIXATION

Most surgeons suture drainage devices to the sclera with nonabsorbable 7-0 to 9-0 nylon or polypropylene to keep the plate from migrating (Fig. 45–2C). Because the sclera is relatively thin posterior to the rectus muscle insertions, optimum visualization and exposure is essential to minimize the possibility of scleral perforation. Specific techniques include using a small-caliber needle [a TG 100-8 or a BV-1 (Ethicon, Inc., Somerville, New Jersey)], placing the sutures first in the sclera and then in a second pass through the fixation hole, or simply preplacing the sutures prior to inserting the explant. Any unexpected bleeding should raise the possibility of perforation with a retinal hole and prompt immediate, indirect ophthalmoscopy, with appropriate treatment, if necessary.

TUBE LIGATION PLACEMENT (NONVALVED TUBES)

Nonvalved devices implanted in one procedure without tube occlusion almost always reduce IOP to below physiological levels in the early postoperative period. Several modifications in surgical technique and implant design can limit this risk.

Molteno originally recommended a two-stage procedure, beginning with fixation of the plate, followed 8 weeks later by inserting the tube into the anterior chamber.⁴³ However, many surgeons prefer to insert the tube earlier than this, especially since IOP is often uncontrolled between surgeries.

An alternative approach employs temporary occlusion of the tube lumen, using one of several methods (Fig. 45–3A–D). Most of these involve an external ligature, either with or without a removable suture stent.^{39,44–51}

Cooperative patients with good exposure may require only temporary ligation with a 7-0 or 8-0 polyglactin suture. Releasable stents, combined with a standard

polyglactin ligature, provide temporary closure of the tube, yet allow the surgeon to open it at any time after surgery.^{39,45,50,51} These stents, generally a 3-0 to 5-0 nylon or polypropylene suture, may be placed within the tube lumen or alongside the episcleral portion of the tube (see Fig. 45–3A–D). The polyglactin ligature is then tied tightly around both the tube and the stent to close the tube, with the end of the stent either exposed in the fornix or left beneath the conjunctiva. Pulling the stent later releases ligature tension on the tube and restores flow. A chromic suture stent within the tube lumen may only partially dissolve. This makes it difficult to remove and can encourage a sterile hypopyon.⁵² Alternatively, the surgeon can tie a 7-0 or 8-0 nonabsorbable suture around the tube near the tip prior to insertion in the anterior chamber^{46–48} and then disrupt this with the argon or krypton laser, if necessary.

Several techniques exist to help control IOP prior to dissolution of the tube ligature. These include a temporary trabeculectomy to “bridge” the time between surgery and release of the tube ligature. Another maneuver uses a microsharp blade or suture needle to make fenestrations, or “safety valves,” in the extraocular portion of the tube to allow aqueous to escape between the occlusive ligature and the scleral fistula (Fig. 45–4B). Some surgeons use a 20- to 22-gauge needle to make the scleral fistula larger than the silicone tube to allow aqueous to flow around the tube initially.

TUBE INSERTION: LIMBAL APPROACH

Silicone tubing placed into the anterior chamber will tend to straighten over time and cause the tip to “migrate” anteriorly. Therefore, a limbal fistula should be made as posterior as possible, using a 23-gauge disposable needle to create a tight track, which minimizes both aqueous leakage and tube migration.

Following a paracentesis and light cautery, the needle is oriented parallel to the iris plane, with the tip placed bevel up, 0.5 to 1.0 mm posterior to the limbal blue line, and then advanced into the anterior chamber. The surgeon must observe the needle throughout this maneuver to insure proper orientation, the most important factor influencing the final position of the tube.

PEARL... Proper orientation of the needle when making the limbal fistula is the most important factor influencing the final position of the tube in the eye.

Phakic eyes are particularly challenging because the natural tendency to avoid the iris and lens can leave the tube too close to the corneal endothelium. A preoperative laser iridotomy in eyes with relative pupillary block may deepen the anterior chamber and allow more posterior tube placement.

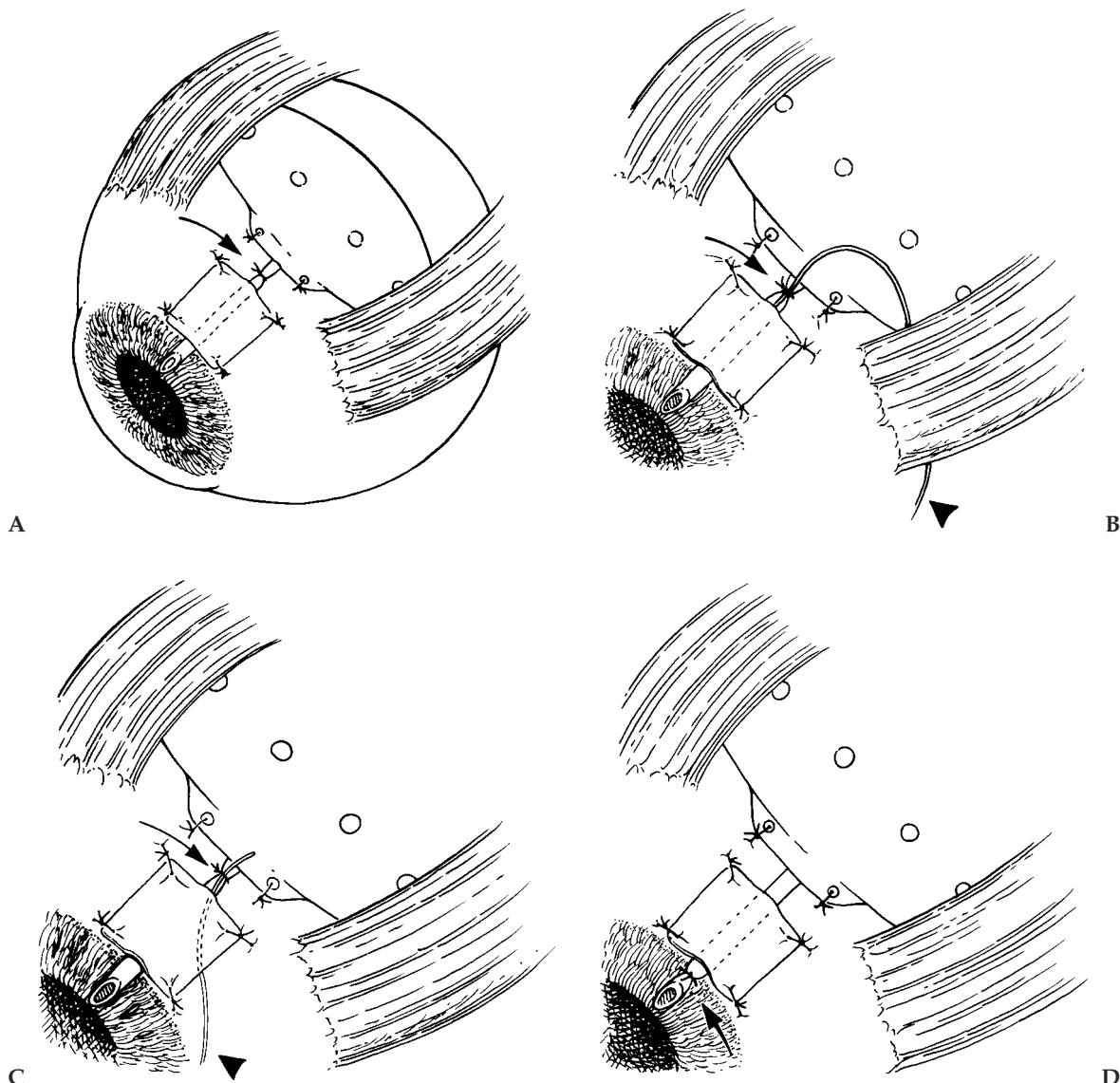


FIGURE 45-3 Tube ligature techniques (arrows) for nonvalved shunts. (A) Posterior, absorbable suture. These ligatures are easiest to lyse if placed just posterior to the graft and 3 to 4 mm anterior to the scleral plate, and 1 to 2 mm closer to the limbus for inferior tubes. (B) Posterior, absorbable suture with releasable intraluminal stent (arrowhead). Looping the stent beneath the adjacent muscle insertion aids removal. (C) Posterior, absorbable suture with releasable stent (arrowhead) tied to the outside of the tube. (D) Anterior, nonabsorbable suture located within the anterior chamber.

Prior to insertion, the tube is trimmed with an anterior bevel to prevent iris incarceration approximately 2 mm beyond the limbus (Fig. 45-2D). Following tube insertion with either a serrated or tube-introducing forceps, the surgeon should reform the anterior chamber and inspect the tube. If too long, it should be removed, trimmed, and reinserted. If the position is unacceptable, it can be removed and reinserted through a new fistula.

Air and balanced salt can be used to help maintain the anterior chamber, although most surgeons prefer viscoelastics. The surgeon should avoid overfilling the anterior chamber and accidentally placing the tube too deep. A properly inserted tube will lie parallel and just anterior to the iris, extending well into the eye (Fig. 45-5A,B).

Aphakic and vitrectomized eyes are prone to immediate softening and scleral collapse, leading to retraction of the tube out of the globe as it expands to physiological pressure after surgery. A similar, but delayed retraction can occur in very young children as the eye grows. The tubing can be cut long, laying some of it on the sclera over a sinuous course for later advancement, if needed.

TUBE INSERTION: PARS PLANA APPROACH

Eyes with obliterated anterior chambers may require tube insertion through the pars plana. This requires a complete vitrectomy either prior to or at the time of tube implantation.⁵³⁻⁵⁹ Because a standard silicone tube tends to rotate

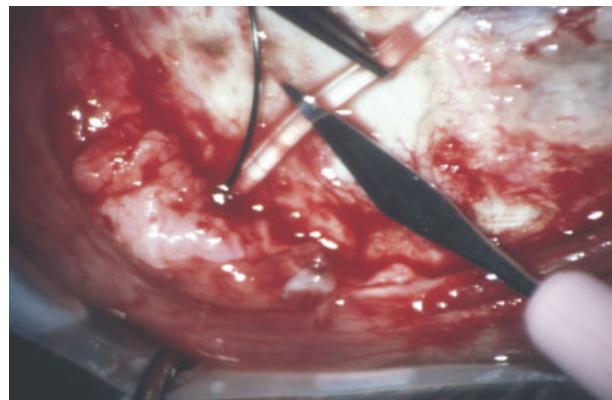
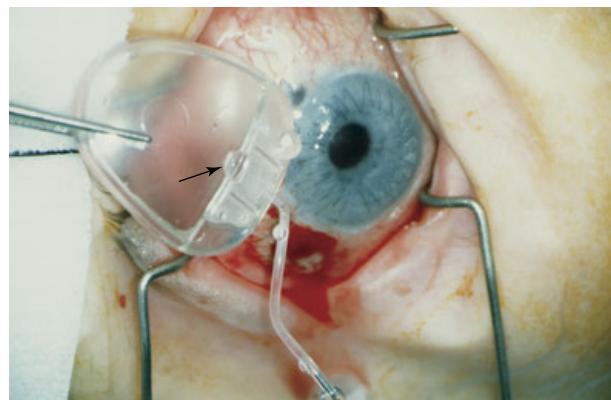


FIGURE 45-4 (A) Valved devices must be “primed” by flushing the tube with balanced salt solution using a 27-gauge cannula. Arrow indicates escape of fluid from the valve portion of an Ahmed glaucoma valve. (B) Fenestration of a tube anterior to the suture ligature using a microsharp blade.

anteriorly, against the lens, this should only be used in aphakic and pseudophakic eyes.¹⁶ The scleral fistula, 3 to 4 mm posterior to the limbus in a normal-sized globe and 2.0 to 2.5 mm in microphthalmic or nanophthalmic eyes, is best made with a 23-gauge needle oriented radially to the visual axis and angled parallel to the iris, or slightly posterior. Orienting the fistula perpendicular to the globe can kink and obstruct the tube. Prior to insertion, the tube should be trimmed 1 mm anterior to the limbus when laid radially over the surface of the globe, with a posterior bevel to prevent obstruction by the iris, lens capsule, or intraocular lens.

The Baerveldt Pars Plana Glaucoma Implant was developed for phakic eyes. This contains a 19.5-gauge silicone sleeve (Hoffman elbow) over the distal end of a standard Baerveldt tube (Fig. 45-1F),⁶⁰ which produces a permanent, 105-degree bend in the tube and prevents kinking and anterior rotation. The angled portion of the sleeve is beveled posteriorly at its tip and fits well through either a pars plana vitrectomy port or a fistula made by a 19- or 20-gauge needle or microvitreoretinal blade oriented perpendicular to the globe.

After pars plana tube insertion, the surgeon should always confirm its position and patency within the vitreous cavity by direct visualization. If not seen, the tube should be removed and reinserted through the same tract after repeat needle fistulization, or through a second fistula.

PATCH GRAFT

Suturing a free patch graft over the anterior portion of the tube and scleral fistula reinforces the limbal tissue and stabilizes the tube within the eye better than a lamellar flap (Fig. 45-2H,I). Surgeons have used many materials for these grafts, including glycerine- or ethyl alcohol-preserved cadaveric sclera⁶⁰ obtained from a local eye bank, and dehydrated cadaveric dura mater,⁶¹ fascia lata,⁶² and pericardium.⁶³ These latter materials, sterilized by solvent dehydration and gamma irradiation, are thin, uniform, and easy to work with and have a long shelf life. Many surgeons prefer to use sclera in children and for tubes placed at the more exposed inferior limbus because it is less likely to dissolve in this relatively exposed region.⁶³

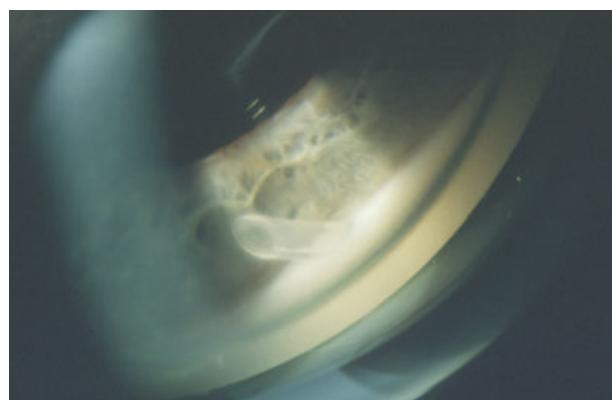
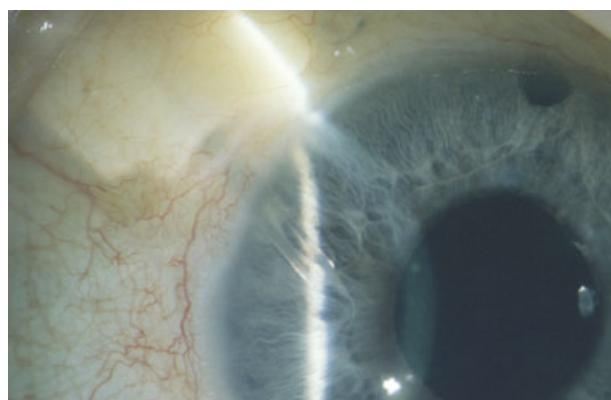


FIGURE 45-5 (A) Proper postoperative appearance of the tube by direct inspection and (B) gonioscopy. The tube is oriented parallel to the iris plane and extends well into the eye with the bevel oriented anteriorly.

The graft, trimmed to approximately 4 mm by 6 mm, is placed with its anterior edge at the original conjunctival insertion, covering the most anterior portion of the tube and the scleral fistula and anchored to the episclera with 7-0 or 8-0 polyglaclin or 10-0 nylon. An anterior bevel on the graft reduces the risk of a postoperative dellen.

CONJUNCTIVAL CLOSURE

Meticulous closure of the conjunctival/Tenon's flap avoids many postoperative complications, including wound dehiscence, conjunctival retraction, tube erosion, explant extrusion, and epithelial ingrowth. Closing a fornix-based conjunctival/Tenon's flap involves anchoring both corners to the limbus using an interrupted 8-0 or 9-0 absorbable material, compressing the conjunctiva tightly over the peripheral cornea, anterior to the patch graft. The relaxing incisions can be closed with running extensions of the anchoring sutures, or further interrupted sutures. Initially anchoring Tenon's capsule to the scleral surface with an absorbable suture after adequate tissue mobilization can release tension and prevent wound dehiscence.¹⁵ Valved drainage devices need water-tight conjunctival closure, including two-layered closure of the radial relaxing incisions. A limbus-based conjunctival flap also requires a two-layer closure to prevent wound leaks over the patch graft and tube.

ADJUNCTIVE ANTIFIBROSIS

Most surgeons have abandoned Molteno's postoperative systemic antifibrosis regimen.^{64,65} Unfortunately, postoperative subconjunctival 5-fluorouracil injections^{31,32} and intraoperative mitomycin-C³¹⁻³⁵ both appear to increase early postoperative hypotony and poor wound healing. A fornix-based conjunctival flap, which places the incision far from the site of antimetabolite application, may limit the occurrence of wound dehiscence and implant extrusion. Although we lack long-term trials, these agents do not seem to improve long-term IOP control with aqueous shunts, and they may not be worth the increased risk of complications.

POSTOPERATIVE MANAGEMENT

POSTOPERATIVE MEDICATIONS

Standard postoperative medications include topical antibiotics, corticosteroids, and long-acting cycloplegics. Intraocular inflammation often increases following ligature release and may require a temporary increase in topical corticosteroids for several days. If glaucoma medications are required immediately after implantation of a ligated nonvalved device, many surgeons prefer rapidly reversible agents, such as topical alpha₂ agonists or carbonic anhydrase inhibitors, which can be stopped quickly once the occluding suture relaxes.

TUBE LIGATURE RELEASE

In general, the surgeon should delay the release of an occluding ligature until after formation of the fibrous capsule, which usually occurs by 3 to 4 weeks, and as long as possible in eyes at high risk for complications from hypotony. Reduction of IOP to the low single digits almost always occurs immediately after the tube opens. Return to a more physiological level can take several days to a week, depending on the health of the ciliary body.

Laser lysis of an interrupted polyglaclin ligature with either the argon or krypton laser requires a Hoskins or similar style lens to compress the overlying conjunctiva and blanch the conjunctival vessels. Several applications with a duration of 0.05 seconds, 500 to 600 mW power, and a spot size of 50 μm are generally adequate, and the globe should be inspected and IOP checked frequently. The appearance of subconjunctival fluid and increased anterior chamber reaction often indicates a successful treatment. If necessary, the suture can be surgically released through a small conjunctival/Tenon's capsule incision.

Removing a releasable nylon or polypropylene suture requires gentle, steady traction on the suture, parallel to the tube, to avoid distorting its position. A persistent IOP elevation suggests temporary obstruction at the site of the absorbable ligature by fibrin, clotted blood, or other material.

EARLY POSTOPERATIVE COMPLICATIONS (FIRST 3 MONTHS) (TABLE 45-3)

ELEVATED INTRAOCULAR PRESSURE

Immediately after implantation of a nonvalved, ligated drainage device, the IOP is often elevated to its preoperative level, or higher. When the ligature releases, the pressure falls rapidly and then recovers over the next 1 to 2 weeks. In contrast, valved devices usually produce a low, but measurable, pressure immediately after surgery, with a gradual rise over the next several weeks. With either type of device, further elevation of IOP results from either a "hypertensive" response, or obstruction of the tube itself.

A "hypertensive phase" consists of a transient IOP elevation, rarely above 30 mm Hg.^{7,12,23} This probably results from inflammatory changes in the fibrous capsule, which increase the resistance to passive diffusion of aqueous. Over time, the IOP often spontaneously decreases due to remodeling of the capsule. However, aqueous suppressant medications may be needed to protect the optic nerve, and may also facilitate capsule remodeling and long-term IOP control.

IOP elevations greater than 30 mm Hg indicate a possible tube obstruction,^{7,12,23} generally accompanied by the absence of a fluid-filled capsule overlying the drainage plate. Obstruction of the tip and intraocular portion of the tube is generally apparent on direct slit-lamp examination, although pars plana tubes may be more difficult to visualize.

TABLE 45-3 COMPLICATIONS OF AQUEOUS SHUNTS

<i>Complication</i>	<i>Cause</i>
Early	
Increased IOP	Tight ligature “Hypertensive phase” (IOP < 30 mm Hg) Tube obstruction (at the tip/persistent ligature valve) (IOP > 30 mm Hg) Kinking of standard tube in pars plana insertion Failure to prime a valved device
Hypotony	Incomplete ligation Improper valve function Inflammation and aqueous hyposecretion Ligature release
Wound dehiscence, conjunctival retraction	Children Inferior implants Incomplete wound closure Limbus-based conjunctival flap Epithelial ingrowth
Tube touch (cornea/crystalline lens)	Improper needle orientation for fistulization Poor tube fixation at limbus Postoperative anterior chamber shallowing
Tube retraction	Physiologic expansion of the globe with short tube Inadequate scleral fixation of the drainage plate
Late	
Increased IOP	Thickened capsule wall Valve leaflet fusion (Ahmed) Fibrous “capping” of proximal tube tip
Tube erosion	Inadequate patch graft Excessive exposure
Tube retraction	Growth of the eye (children <3 years old)
Strabismus	Stretching or tethering of extraocular muscles by expanded capsule Scarring of superior oblique tendon (superior nasal placement)

Tube obstruction can occur anywhere from the tip of the tube to the scleral plate. Clotted blood or fibrin, vitreous, iris, lens material, iridocorneal endothelial membranes, and fibrous or neovascular membranes may all occlude the ostium of the tube within the eye. Obstruction within the tube lumen usually results from clotted blood or fibrin. Early obstruction may also occur in eyes with excessive intraocular inflammation^{37,38,66,67} and from failure to prime a valved device at the time of insertion.

Meticulous orientation of the needle during fistulization and carefully placing the tube away from potentially obstructing structures can generally avoid occlusion of the tube tip. When occlusion does occur, management consists of removing the obstructing material. Argon laser burns using a large spot size (e.g., 300 to 500 μm), low power (200 to 400 mW), and long duration (0.3 to 0.5 sec) can contract and pull incarcerated iris from the distal ostium.⁶⁸ The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser can occasionally eliminate blockage by vitreous,⁶⁹ iris, fibrin, and fibrous, neovascular, and iridocorneal-endothelial membranes.⁷⁰ Unfortunately, these treatments are often followed by reocclusion of the tube.

Intensive corticosteroid eyedrops and firm, digital pressure to the globe or gentle massage over the tube

often help resolve clotted blood or fibrin. If the tube appears to be clear, simple digital pressure on the globe or manipulation of the conjunctiva overlying the tube and the valve mechanism with a cotton-tipped applicator may dislodge the obstructing material within the tube.⁷¹ Occasionally, tissue plasminogen activator (3 to 5 μg) injected either into the anterior chamber or the tube itself is necessary to resolve a persistent clot,^{36-38,66,67,72} but this should not be used in eyes with recent intraocular bleeding. Some situations require surgical removal of the obstructing material from the anterior chamber, “exploration” of the tube for obstruction with a 4-0 nylon suture,⁷² repositioning the tube, or replacing the entire device.

HYPOTONY

Pressure in the single digits is not uncommon immediately after implantation of a valved device, although some patients experience excessive flow and profound hypotony. Following installation of a ligated, nonvalved tube, early hypotony can result from incomplete occlusion of the tube, leakage through a large scleral fistula, or excessive flow through a tube fenestration. With either type of device, severe inflammation from the surgery or initial

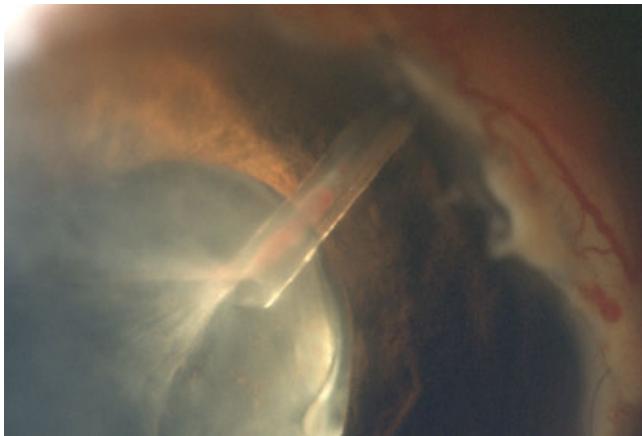


FIGURE 45-6 Fibrinous anterior chamber inflammatory reaction following tube ligature release.

hypotony with choroidal effusions can lead to a vicious cycle of aqueous hyposecretion and persistent hyptony.

In nonvalved devices, release of the tube ligature generally produces a second episode of hypotony, usually into the single digits (Fig. 45-6). This situation requires intense corticosteroids and discontinuing aqueous-suppressant medications.

Eyes with ciliary body dysfunction from uveitis, ocular ischemia, or prior cyclodestructive surgery are at particular risk of developing chronic hypotony.^{42,73} Such persistent hypotony may require permanent ligation or complete removal of the tube from the anterior chamber and closure of the scleral fistula.

WOUND DEHISCENCE AND CONJUNCTIVAL RETRACTION

Breakdown of the conjunctival wound can lead to wound leaks, exposure of the scleral graft or tube, or epithelial ingrowth into the subconjunctival space. Meticulous, watertight conjunctival closure, particularly when the aqueous can access the subconjunctival space, minimizes the occurrence of these problems.

Early retraction of the anterior edge of a fornix-based conjunctival flap is most common in children and in adults with extensive conjunctival scarring. Placing the patch graft anterior to the tube insertion and the conjunctival/Tenon's flap anterior to this may minimize exposure of the tube or scleral fistula. In mild cases, applying frequent topical lubricants, reducing topical steroids, and avoiding repeated trauma will generally stabilize the retraction and allow epithelialization of the exposed surfaces. Excessive retraction or exposure of the silicone tube may require more extensive surgical revision.

Recurrent wound dehiscence, particularly with an aqueous leak, suggests epithelial ingrowth into the subconjunctival space and bleb capsule.¹⁵ This is more likely to occur in patients with extensive conjunctival scarring and a limbus-based flap, which necessitates placing the

wound directly over the graft or tube itself. Such patients usually require more extensive revision, meticulous epithelial debridement and cryotherapy, and, often, removal of the drainage device.

PITFALL... Recurrent wound dehiscence, particularly with an aqueous leak, suggests epithelial ingrowth into the subconjunctival space and bleb capsule and may lead to plate extrusion or epithelial invasion of the anterior chamber.

TUBE-CORNEA TOUCH

Contact between an anterior chamber tube and the corneal endothelium usually results from improper tube positioning (usually from faulty needle orientation) or postoperative alterations in anterior chamber anatomy. This occurs more commonly in phakic patients, who have shallower anterior chambers. An excessively long tube that is improperly oriented may also damage the corneal endothelium. These problems can be corrected by shortening the tube or by surgically redirecting it away from the cornea.^{74,75}

Postoperative shallowing of the anterior chamber with tube–cornea touch may result from hypotony, serous or hemorrhagic choroidal detachments, or aqueous misdirection.⁷⁶ In general, reversing the underlying cause will result in posterior movement of the lens–iris diaphragm and tube. Occasionally, direct contact with the corneal endothelium necessitates immediate deepening of the anterior chamber with a viscoelastic, and drainage of a choroidal effusion, anterior hyaloidotomy, or pars plana vitrectomy, as indicated by the situation.

TUBE RETRACTION

Retraction of the tube from the anterior chamber may occur either early or late. During the first few postoperative days to weeks, an initial collapse, followed by physiological expansion of the globe, may gradually draw the tube out of the eye. Movement of the drainage plate due to inadequate scleral fixation and migration from maturation of the fibrous capsule can produce delayed retraction, as can growth or pathological expansion of the eye in very young children.

Intraoperative techniques for preventing tube retraction in these situations have already been discussed. In general, no intervention is necessary as long as the tube is visible in the eye and the IOP is normal. Complete retraction of the tube from the eye produces marked elevation of IOP and may respond to reinserting the tube through a new limbal fistula,⁷⁷ or into the posterior chamber, combined with a vitrectomy. Tube extension with reinsertion through the original fistula involves transecting the tube and interposing a larger-bore silastic tubing between the proximal end and a second piece of tubing.⁷⁸

LATE POSTOPERATIVE COMPLICATIONS (AFTER 3 MONTHS)

ELEVATED IOP

Gradual loss of IOP control after surgery usually results from progressive thickening of the fibrous capsule and increased resistance to aqueous diffusion. This generally produces a large cystic bleb over the scleral plate, visible by either slit-lamp biomicroscopy or B-mode echography (Fig. 45-7A,B). Although this situation often responds to glaucoma medications, surgical revision may be necessary, either by needling through the conjunctiva⁷⁹ or by direct excision of the bleb capsule. Both should be delayed for at least 6 to 9 months to allow remodeling of the capsule and a spontaneous decrease in IOP.

Transconjunctival revision is best performed under an operating microscope, using subconjunctival anesthesia. This consists of entering the conjunctiva 5 to 10 mm from the capsule with a hypodermic needle or a needle-knife and puncturing the capsular wall using lateral, cutting motions. Appearance of subconjunctival fluid and softening of the globe indicate successful opening. Postoperative 5-fluorouracil injections, or pre-operative, low-dose mitomycin-C, as described for similar revisions of scarred filtering blebs after trabeculectomy,⁸⁰ may also be considered. However, limited clinical data have not yet demonstrated that this is highly beneficial.^{79,81,82}

Surgical excision generally requires retrobulbar anesthesia and parenteral sedation. Using either a limbal or fornix incision, the capsule is exposed and then treated with mitomycin-C (0.2 to 0.5 mg/mL) soaked on a piece of surgical sponge for 3 to 5 minutes, followed by copious irrigation. A large piece of the superior capsule wall is then excised, followed by conjunctival closure and reformation of the anterior chamber. Nonvalved devices require tube constriction with an absorbable ligature to minimize early postoperative hypotony.

Fusion of the valve leaflets may cause a late pressure rise following Ahmed valve implantation.⁸³ However, the most common cause for tube obstruction in this time frame is fibrous capping of the proximal ostium at its junction with the drainage plate, which is more common with valved devices.^{16,23,84,85} Late obstruction by mature fibrous tissue generally requires removal of the scar tissue or repositioning of the tube.^{16,23}

TUBE EROSION

Erosion of the tube through the overlying conjunctiva can occur either at the limbus or anywhere along the tube or scleral plate. The surgeon can minimize the incidence of this complication by avoiding placement of the tube in the interpalpebral zone, using donor sclera in patients at particular risk for tube erosion and in young patients, and properly placing the patch graft over the anterior portion of the tube and fistula.

Patch grafts often thin over time, but this generally does not produce erosion through the conjunctival surface (Fig. 45-8A,B). However, complete exposure of the tube carries a high risk of progressive conjunctival breakdown, aqueous leak, and endophthalmitis. This should be repaired immediately by mobilizing the adjacent conjunctiva, placing a new patch graft, and advancing healthy conjunctiva over the tube and graft.

STRABISMUS

Several reports describe the development or exacerbation of strabismus following installation of glaucoma drainage devices.^{86–93} In many patients, the muscle imbalance and associated symptoms lessen with time. Most of these ocular deviations are vertical^{86,87,90,91} and are often reported following placement of a drainage device in the superonasal quadrant.^{88,92,93} Mechanisms for strabismus include excessive stretching of a rectus muscle away from the globe by the underlying bleb capsule,⁸⁹ and posterior

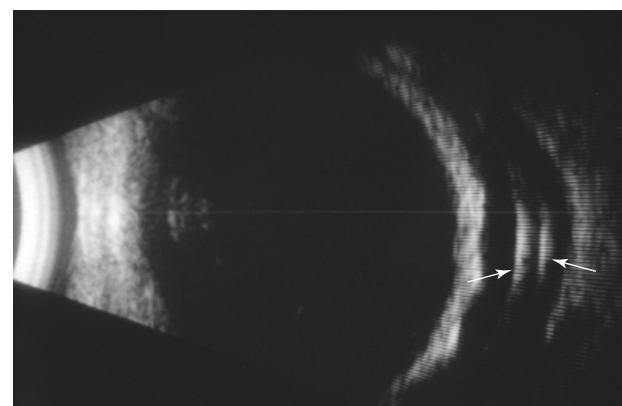
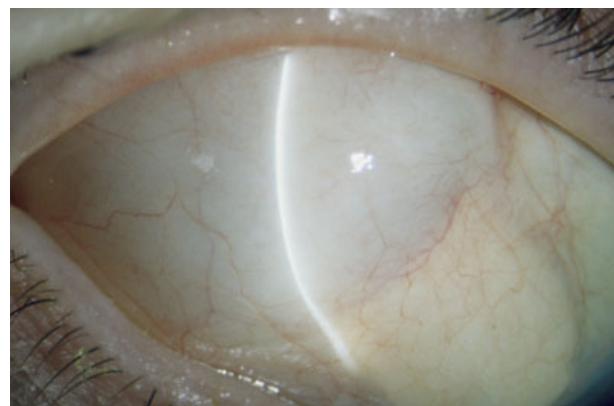


FIGURE 45-7 (A) Encapsulated bleb surrounding an explant, as seen by biomicroscopy and (B) ultrasonography, associated with late, persistently elevated IOP. Arrows in (B) indicate the upper and lower edges of the plate.

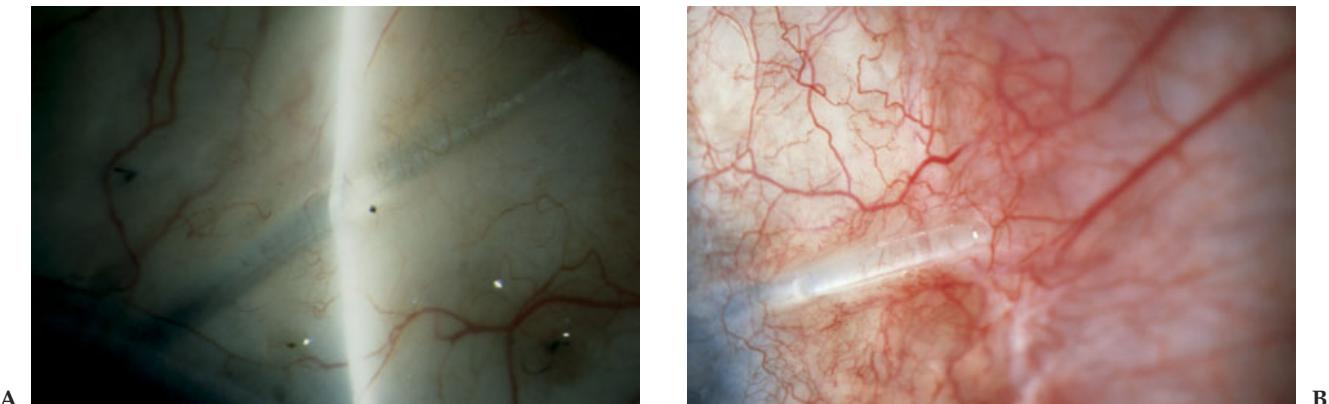


FIGURE 45-8 (A) Patch grafts often will erode away over months to years, leaving the tube immediately beneath the conjunctiva. (B) Erosion of the tube through the conjunctiva. [(B) courtesy of Dale Heuer, M.D.]

fixation of the muscle by scar tissue from the bleb capsule.^{87,89,92} Other causes include adherence due to orbital fat⁸⁶ and scarring or tucking of the superior oblique tendon by devices placed in the superonasal quadrant, resulting in a pseudo-Brown's syndrome.^{92,93}

Surgical correction of strabismus after aqueous shunts is generally difficult and may jeopardize IOP control. Because of this, prevention remains the best treatment for motility dysfunction. For this reason, the Baerveldt implant now contains multiple fenestrations in the scleral plate, which allow fibrous tissue to grow through the plate and limit the ultimate height of the bleb.⁸

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OCULAR HYPOTONY

Mary G. Lynch, M.D., and Reay H. Brown, M.D.

Ocular hypotony is a serious, sight-threatening condition. Although trauma and inflammation can also produce hypotony, filtration surgery is now its leading cause. This is due to recent trends toward more aggressive surgical management of glaucoma and the widespread use of antifibrosis agents, which increase the occurrence of excessive, leaking, and overfiltrating blebs.

Hypotony shortly after filtration surgery is common and can generally be managed conservatively. However, prolonged hypotony and its sequelae, such as hypotony maculopathy and lens–cornea touch, require aggressive, often surgical, management. Numerous techniques are now available for treating both bleb leaks and overfiltration, and their use depends on the etiology and duration of these abnormalities. Although hypotony often resolves with time, the long-term outcome of its sequelae is guarded. The best treatment remains prevention, with judicious choice and use of surgical techniques. If hypotony maculopathy does occur, aggressive, early reversal of the hypotony offers the best hope of visual recovery, often requiring the surgeon to choose visual acuity over bleb function.

The definition of ocular hypotony has ranged from 2 to 10.5 mm Hg, although clinical studies now often use a pressure below 6 mm Hg.^{1,2} However, some eyes remain asymptomatic despite extremely low intraocular pressures (IOPs), whereas others experience sight-threatening complications at pressures that are well within the low-normal range. Rather than using an absolute numerical pressure, it is best to define “clinical hypotony” as a pressure low enough to cause functional and structural changes that reduce visual acuity. This actual pressure level will vary for each patient, depending upon other factors such as age, refractive status, and race.

PEARL... Clinical hypotony is a pressure low enough to cause functional and/or structural changes that reduce visual acuity.

CLASSIFICATION OF OCULAR HYPOTONY

Hypotony is generally classified as related or unrelated to the presence of a filtering bleb. Hypotony following filtering surgery can be further categorized by its timing in relation to the surgery and the extent of anterior chamber shallowing. All of these considerations help direct both the timing and the approach to therapy.

Bleb-related hypotony results from either excessive overfiltration or from a leak in the bleb. Since the introduction of adjunctive antifibrotic agents with filtering surgery, the incidence of hypotony has doubled, from 10 to 15% of eyes undergoing trabeculectomy to as high as 32%.^{1,3,4} Histopathology of these blebs shows diminished numbers of fibroblasts and disorganized, widely spaced collagen fibrils.⁵ Many lack blood vessels entirely, giving them their characteristic, bone-white appearance (Fig. 46-1). Independent of the bleb, other factors that can contribute

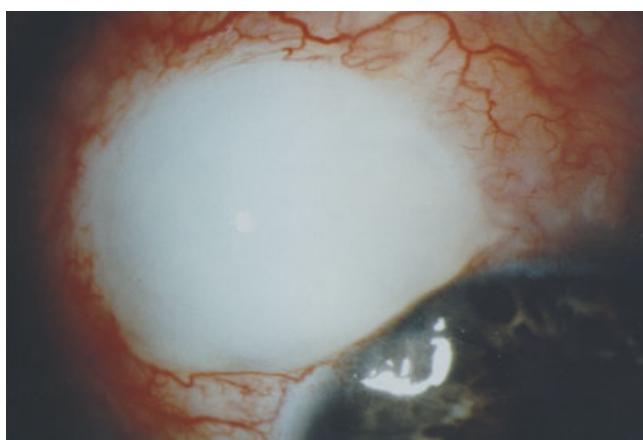


FIGURE 46-1 Filtering surgery with an adjunctive antifibrotic agent often results in blebs that are thin, avascular, and prone to leaking or overfiltration.

to hypotony include inflammation, a cyclodialysis cleft, and ciliary body "shutdown."

Because many eyes exhibit transient and uneventful low pressure shortly after filtration surgery, hypotony in the early postoperative period requires more conservative management than that which develops later or persists for weeks or months. Similarly, shallowing of the anterior chamber generally recovers and can be approached more conservatively than if there is lens–cornea touch.

SEQUELAE OF DELAYED OR PROLONGED OCULAR HYPOTONY

Filtering surgery commonly results in a transient low pressure. However, hypotony that persists for several weeks to months, or develops long after the filtering procedure, can lead to sight-threatening sequelae. The most serious of these is hypotony maculopathy (Fig. 46–2A,B).

In hypotony maculopathy, low IOP leads to chorioretinal folds in the macula, optic disc swelling, and, occasionally, a peripheral choroidal detachment (Table 46–1).^{6–9} Animal studies have shown that hypotony can disrupt axonal cytoarchitecture and slow axonal transport.¹⁰ Symptoms include decreased central visual acuity and metamorphopsia, which some patients describe as "looking through Venetian blinds" or a cracked window.

Hypotony maculopathy generally does not occur if the pressure is greater than 6 mm Hg. However, patients can describe visual aberrations with pressures in the 8 to 12 mm Hg range. Because the fundus can appear relatively normal or be obscured by hazy media due to the hypotony, a fluorescein angiogram may help reveal a wrinkled posterior pole.

Although the incidence of hypotony, as defined by IOP, after filtering surgery can be as high as 32%, only about 14% of patients will develop clinical maculopa-

TABLE 46-1 HYPOTONY MACULOPATHY

Symptoms	Decreased central acuity Metamorphopsia
Signs	Low intraocular pressure (generally less than 6 mm Hg) Chorioretinal folds in the macula (may require fluorescein angiography) Optic disc swelling Peripheral choroidal detachment

thy.^{2,4,6,11} However, early recognition of this complication is important. In general, reversal of maculopathy is inversely related to the duration of the hypotony,^{3,12} and pressure should be restored to the normal range, or above, within several weeks of developing posterior pole changes.

Although hypotony maculopathy generally occurs shortly after filtering surgery with antimetabolites, it can also develop long after the procedure. Additional risk factors include young age,^{6,8,12,13} myopia,^{6,8,13} Caucasian race,⁶ and previous exposure to carbonic anhydrase inhibitors.¹² The risk of developing hypotony maculopathy is lower in African Americans,¹¹ probably due to their overall decreased incidence of hypotony after filtering surgery.¹⁴

Other sequelae of prolonged hypotony include cataract formation, corneal edema,¹⁵ fixed folds in the retina, visual field loss,⁹ bleb infections, and endophthalmitis.^{16,17}

HYPOTONY INDEPENDENT OF BLEB PATHOLOGY

INFLAMMATION

Inflammation following either filtration surgery or trauma can produce hypotony through iridocyclitis, ciliochoroidal detachment, and traction detachment of the ciliary body.

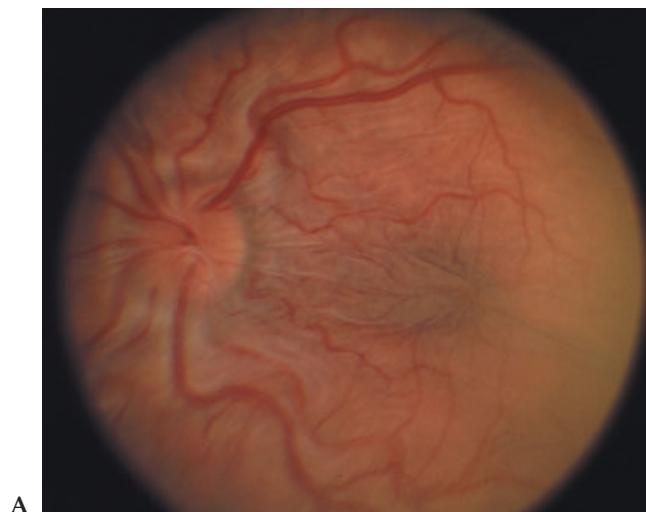
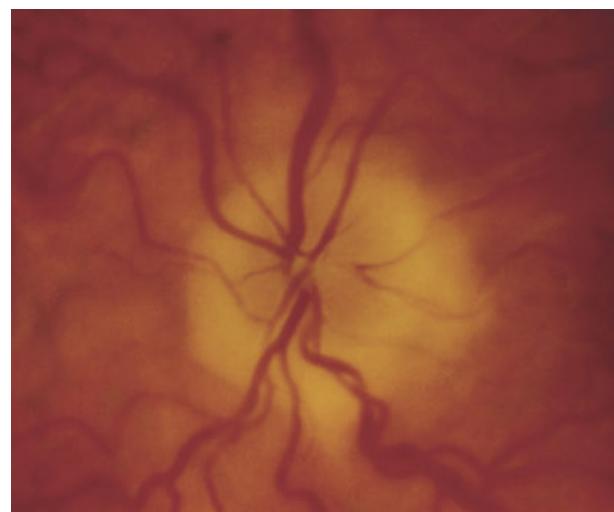


FIGURE 46-2 (A) In hypotony maculopathy, the posterior pole often shows a diffuse pattern of chorioretinal folds as well as (B) optic nerve swelling.



B

Iridocyclitis may both diminish aqueous production and enhance uveoscleral outflow.^{18,19} Treatment usually includes topical steroids and cycloplegia, and systemic steroids in cases with severe inflammation or ciliary body detachment.

Ciliochoroidal detachments, which diminish aqueous humor production, can occur in up to 34% of eyes after filtering surgery^{15,20} and usually result from inflammation, an overfiltering bleb, or both. Although large detachments are easily seen by direct or indirect ophthalmoscopy, ultrasound biomicroscopy may be required to detect anterior or diffuse detachments.²¹ Usually, topical and systemic steroids, as well as cycloplegics, are necessary to resolve a choroidal detachment caused by inflammation. When an overfiltering bleb is the cause, treatment usually requires correcting the underlying problem.

Inflammation can also cause ciliary body traction and detachment by encouraging membrane formation in the anterior vitreous cavity. In the setting of proliferative vitreoretinopathy, such membranes must be removed by pars plana vitrectomy and membrane stripping.²¹⁻²⁴

CYCLODIALYSIS CLEFT

A cyclodialysis cleft, or separation of the ciliary body from the scleral spur, creates hypotony by allowing the escape of aqueous through the cleft into the suprachoroidal space. This can produce diffuse choroidal thickening or a bullous choroidal detachment. These clefts usually result from blunt or penetrating trauma. However, they may also complicate cataract or filtration surgery, generally from inadvertent manipulation and/or traction of the iris or incisional entry posterior to the scleral spur. These clefts are usually located close to the surgical site.

Diagnosis of a cyclodialysis cleft is often complicated by coexistent corneal edema, hyphema, and shallowing of the anterior chamber, all of which impede its visualization by gonioscopy. These obscure clefts can be identified using ultrasound biomicroscopy^{25,26} or by deepening the anterior chamber with a viscoelastic prior to gonioscopy.²⁷ A more invasive approach involves injecting balanced salt solution with added fluorescein into the anterior chamber and recovering fluorescein-stained fluid from the supraciliary space through a sclerotomy.²⁸

PITFALL... Coexistent corneal edema, hyphema, and shallowing of the anterior chamber can all prevent gonoscopic detection of a cyclodialysis cleft.

The literature describes many procedures for treating cyclodialysis clefts, providing strong testament to the difficulty of treating this condition (Table 46-2). Clefts that occur shortly after surgery occasionally close following cycloplegia and termination of topical steroids. In cases with good visualization, several investigators

TABLE 46-2 MANAGEMENT OF CYCLODIALYSIS CLEFTS

Cycloplegia and discontinuation of steroids
Direct photocoagulation using a gonioprism: argon laser
Cryotherapy
Indirect photocoagulation
Diode laser
Trans-scleral yttrium-aluminum-garnet (YAG) laser
Diathermy
Suturing
Nonvisualized passage
Direct cycloectomy
Pars plana vitrectomy, cryotherapy, gas tamponade

have reported success with direct argon laser photocoagulation through a gonioprism,^{27,29,30} often with a peribulbar anesthesia. Confluent applications of 100 µm spots at 0.1 to 0.2 sec and 500 to 1000 mW are delivered to the base of the cleft, followed by postoperative cycloplegics. Some cases require repeat treatments to progressively close the cleft.

Poorly visualized clefts can be treated indirectly from the outside by cryotherapy, or photocoagulated with either a diode or trans-scleral yttrium-aluminum-garnet (YAG) laser.³¹⁻³³ Diode laser treatment uses the contact hand piece (G-probe) to deliver two rows of 1500 mW contiguous applications for 1500 msec each over the cleft, beginning 1.5 mm posterior to the limbus. All of these indirect approaches require a local anesthetic block for comfort, and postoperative cycloplegics.

More aggressive surgical therapy involves external diathermy to the bed of a scleral flap that is created over the cleft.^{28,34} This can be combined with suturing the cleft closed with 9-0 or 10-0 nylon through the scleral bed,³⁵ either with or without direct visualization.^{36,37} Particularly recalcitrant clefts may require pars plana vitrectomy, cryotherapy, and tamponade with sulfur hexafluoride gas.^{38,39}

Once a cleft is closed, the eye can experience a period of extremely high pressure. Commonly, the patient undergoes treatment and is sent home with cycloplegia, only to call the surgeon several hours later in tremendous pain. The surgeon should always warn the patient of this possibility and consider prescribing prophylactic aqueous suppressants.

SPECIAL CONSIDERATION

Shortly after a cyclodialysis cleft is closed, the eye often goes through a period of extremely high pressure that is accompanied by tremendous pain.

CILIARY BODY SHUTDOWN

Ciliary body shutdown can occur after filtering surgery if the eye is treated with an aqueous suppressant. This has been reported with topical beta-blockers, and both topical and systemic carbonic anhydrase inhibitors.⁴⁰⁻⁴³ This phenomenon, usually associated with a choroidal detachment, probably results from drug supersensitivity because discontinuing the medication usually resolves the hypotony.

Ciliary body shutdown and aqueous suppression may also result from the toxic effects of antifibrotic agents on the ciliary body.^{44,45} These findings may help explain the higher incidence of hypotony following the use of antimetabolites.

HYPOTONY SECONDARY TO BLEB PATHOLOGY

In the early postoperative period, up to one third of eyes experience overfiltration and a low IOP (i.e., less than 6 mm Hg).⁴⁶ In the absence of lens–cornea touch and massive choroidal detachment, the hypotony will generally resolve and require only topical steroids and cycloplegics. Surgical intervention is needed if the cornea or retina is in jeopardy, or if the hypotony persists or develops later in the postoperative period.

PATHOGENESIS OF OVERFILTERING BLEBS

Aqueous Production

Proper development of filtering blebs depends, in part, on continued production of aqueous humor. Limiting aqueous production, especially in the early postoperative period, can reduce the height of a bleb, and ultimately its function.

Surgical Bleb Construction and Postoperative Management

Several factors during and after surgery significantly influence the behavior of a filtering bleb: (1) assessment of conjunctival integrity, (2) flap construction, (3) sclerectomy size, (4) antimetabolite use, (5) preservation of Tenon's capsule, (6) intraoperative assessment of the conjunctival wound for leaks, and (7) timing of suture-lysis.

By evaluating the thickness and integrity of the conjunctiva with a wet cellulose sponge, the surgeon can identify residual conjunctival scars and choose a different site for the incision, if possible. Eyes with thinner conjunctiva and Tenon's capsule may require a lower concentration of antimetabolite or a shorter exposure time.

In general, a thin flap offers less resistance to aqueous outflow than a thicker flap. Large sclerectomy holes also

enhance aqueous outflow, as do holes located close to the edge of the scleral flap. In a highly myopic eye, the surgeon should make the sclerectomy small relative to the flap size. Alternatively, a relatively thick scleral flap can allow for a more generous sclerectomy. A corneal safety-valve incision, using a narrow scleral flap tunneled anteriorly into clear cornea, may result in less hypotony.⁴⁷

Antifibrosis agents should be used with caution, particularly in young myopes and other individuals at high risk for complications from hypotony. This includes substituting 5-fluorouracil for mitomycin in primary filters.

If there are any concerns about possible overfiltration postoperatively, the surgeon should close the flap with several sutures. Extra sutures generally provide greater flexibility in suture lysis, which can be performed sequentially, allowing adequate time to assess its effect. Antimetabolites can allow the surgeon to delay suture lysis or removal by up to 2 months after surgery.⁴⁸

Bleb Instability, Evolution, and Repetitive Trauma

The structure and function of filtering blebs can also change years after the surgical procedure.⁴⁹ A "stable," well-functioning bleb can evolve into a large, avascular bleb that causes hypotony despite years of adequate pressure control. Most of these changes result from the continued internal pressure of aqueous outflow against the unstable, weak conjunctiva.

PEARL... Over time, a "stable," well-functioning bleb can become a large, avascular bleb that causes hypotony despite years of adequate pressure control.

External, repetitive trauma, such as chronic eye rubbing by the patient or inadvertent pressure during sleep, also can cause a bleb to extend and become thinner and multilobulated. Any case of excessive filtration should suggest a history of trauma or ocular irritation producing continued rubbing or scratching.

PATHOGENESIS OF LEAKING BLEBS

"Traumatic" tears usually occur from a single event, such as an injury. These bleb tears usually appear as slits or flaps, and their edges are often relatively "raw." They usually heal with aqueous suppression and patching.

Atrophic holes generally develop in thin, avascular conjunctiva. This type of leak looks more like a "hole" with a raised cuff around the opening. Because the edges of the opening may be lined with conjunctival epithelium, these threadbare holes generally require more aggressive surgical intervention than acute tears.

MANAGEMENT OF EARLY OVERFILTRATION

Transient overfiltration and hypotony commonly occur 2 to 3 days after filtering surgery.⁴⁶ Most eyes without lens–cornea touch or marked choroidal detachment respond well to conservative management. However, a persistent, shallow anterior chamber may encourage peripheral anterior synechia formation, damage to the corneal endothelium, cataract formation, and filter failure. Decreased steroids and the addition of strong cycloplegics, such as atropine, usually help deepen the anterior chamber.

If these medical maneuvers are ineffective, a compression, or “torpedo,” patch placed over the scleral flap can help deepen the anterior chamber. This type of patch consists of the inner cotton from an eye pad, rolled into a tube shape and folded in half. This is then placed on the closed eyelid directly over the bleb, and held in place with two or three eye pads.

Oversized bandage contact lenses, available in diameters up to 24 mm, can also be used to tamponade the flap.⁵⁰ The lens is placed on the eye and the patient checked every 2 days for removal and cleaning of the lens and IOP measurement. The average duration of a bandage lens for overfiltration is about 7 days.

The Simmons’ shell can also tamponade a brisk filter.⁵¹ This is a fenestrated methylmethacrylate lens with an internal ledge that depresses the bleb when placed over the cornea, followed by an eye patch. A large-diameter bandage contact lens flattened with peripheral radial incisions can minimize irritation from the shell itself. A large, brisk, or recalcitrant leak should be sutured with either 10-0 nylon or Bisorb, or 9-0 monofilament Vicryl, using a vascular, noncutting needle.

Shallow anterior chambers that do not resolve spontaneously generally require surgical reformation using a viscoelastic agent, occasionally combined with surgical revision of the flap. Eyes with lens–cornea touch can quickly develop corneal endothelial cell damage and require this aggressive approach relatively early.

PEARL... The best treatment for overfiltration is to avoid it.

The best approach to early overfiltration is to avoid it. This requires meticulous surgical technique including careful closure of the flap, sparing use of antifibrotic agents, and evaluation of the surgical wound for leaks.⁵² Suture lysis also should be delayed, preferably for several days after surgery.^{52,53}

MANAGEMENT OF PROLONGED HYPOTONY

In general, a conservative, nonsurgical approach is appropriate (1) for acute bleb tears, (2) for a monocular patient with adequate vision, (3) when central acuity is preserved, (4) for a reliable patient who will notify the physician of any change in symptoms, and (5) for an eye without severe macular changes.

More aggressive, generally surgical, therapy is needed for (1) an eye with a chronic “threadbare” hole, (2) a history of bleb-related infection, (3) an expanding, unstable, overfiltering bleb, (4) a monocular patient with inadequate vision, (5) an unreliable patient for whom repeated trauma is a possibility, and (6) an eye with poor central acuity or marked anisometropia.

MANAGEMENT OF CONJUNCTIVAL LEAKS

The surgeon should always try to repair a conjunctival leak because a leaking bleb is at increased risk of infection and hypotony and will not develop the height necessary to achieve long-lasting filtration (Table 46-3).⁵⁴

Small, early leaks resulting from inadequate conjunctival closure or inadvertent, acute bleb tears often close with aqueous suppression and patching⁵⁵ using either a torpedo cotton pad, an oversized bandage contact lens,^{3,56} or the Simmons’ shell.

Chronic, atrophic holes are more difficult to close and often resist both patching and suturing. Although cyanoacrylate adhesive can seal holes in filtering blebs, a collagen shield or a soft contact lens is often necessary for comfort and to keep the hard glue pellet from tearing the fragile conjunctiva and enlarging the hole.^{57,58}

Atrophic holes often require treatment of the entire bleb to thicken the tissue and induce inflammation. However, the most definitive treatment for a chronically leaking

TABLE 46-3 MANAGEMENT OF CONJUNCTIVAL LEAKS

Patching
Large-diameter bandage contact lens
Simmons’ shell
Aqueous suppression
Topical antibiotics
Cyanoacrylate glue
Suture closure
Fibrin adhesive
Thicken bleb (induce inflammation)
Excise conjunctiva

bleb is conjunctival advancement or transplantation, usually following removal of the thin, avascular portion of the bleb.^{57,59–61}

MANAGEMENT OF PROLONGED OVERFILTERING BLEBS

The choice of technique usually begins with the least aggressive course. However, the stepwise approach discussed here is not an absolute sequence because therapy also depends upon the location and cause of the problem.

Reduce the Extent or Elevation of the Bleb

Continued aqueous production can exert ongoing "barotrauma" to a thin, overfiltering bleb. Decreasing this production with topical and, occasionally, oral aqueous suppressants can "turn down the faucet" and allow some blebs to remodel lower and thicker, particularly in the early postoperative period.

Bleb Compression

Bleb compression with a torpedo patch, an oversized bandage contact lens,^{3,56} or a Simmons' shell can also change the appearance and function of an overfiltering bleb. Such compression can also enhance the effectiveness of more aggressive therapies, discussed in the following text.

Suturing methods can also depress the bleb and tighten the scleral flap. One technique involves placing a 9-0 nylon mattress suture over the bleb, anchored anteriorly in the peripheral cornea and posteriorly in Tenon's and conjunctiva.⁶² The suture is left in place for 1 to 4 weeks and the patient is followed weekly.

Thicken the Bleb

Medical approaches: Reducing or stopping steroids in the early postoperative period can allow the normal inflammation that follows surgery to thicken the bleb. Some topical antibiotics can irritate the conjunctival surface and promote inflammation, but can theoretically select resistant organisms. Trichloroacetic acid, applied to the bleb surface with the end of a small stick, can also shrink and thicken the conjunctival epithelium.⁶³ Unfortunately, these medical approaches are relatively ineffective in treating overfiltering blebs.

Surgical approaches: Argon and YAG laser treatments can effectively stimulate inflammation within filtering blebs. In one approach, the conjunctival epithelium of large, cystic blebs with translucent walls is gently abraded with a cotton-tipped applicator soaked with anesthetic or 95% alcohol, followed by painting with methylene blue to absorb the laser energy.^{64,65} Argon laser applications, 500

to 800 µm in size with a duration of 0.17 to 0.50 sec, are then delivered, titrating the power from 300 to 500 mW to shrink the surface tissue without producing a crater. This technique also works with rose bengal, but has a higher risk of perforating the bleb surface.

A second procedure uses the Lasag Microrupter II neodymium:YAG (Nd:YAG) laser in the continuous wave mode to apply thermal energy to both the surface and base of the bleb.⁶⁶ However, this laser is now generally unavailable.

Cautery⁶⁷ and cryotherapy^{68–70} to the bleb surface have also been advocated for overfiltering blebs. Unfortunately, these methods used alone are frequently ineffective in reversing the hypotony.

Numerous investigators have reported on the efficacy and complications of injecting autologous blood into overfiltering blebs, which encourages fibroblast proliferation and collagen deposition.^{71–77} In this procedure, conducted at the slit-lamp with topical anesthesia, the surgeon draws venous blood from the patient and then puts a new, sterile 30-gauge needle on the syringe. This needle is advanced to the center of the bleb, and blood is injected, often into each of several lobes, if present (Fig. 46-3).

Such injections alone appear to succeed only half the time,^{3,52} although surface cryotherapy, aqueous suppression, and torpedo patching may improve this success rate. Complications include tracking of blood into the eye, which can be averted by first injecting a viscoelastic into the anterior chamber. Increased IOP, corneal blood staining, filter failure, and corneal graft rejection may also occur.

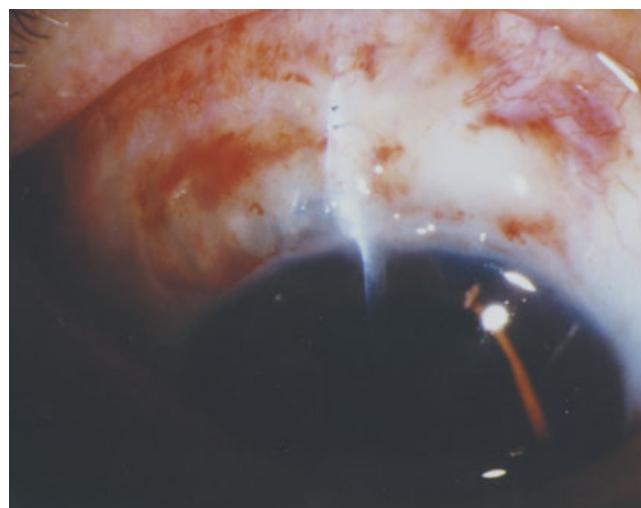
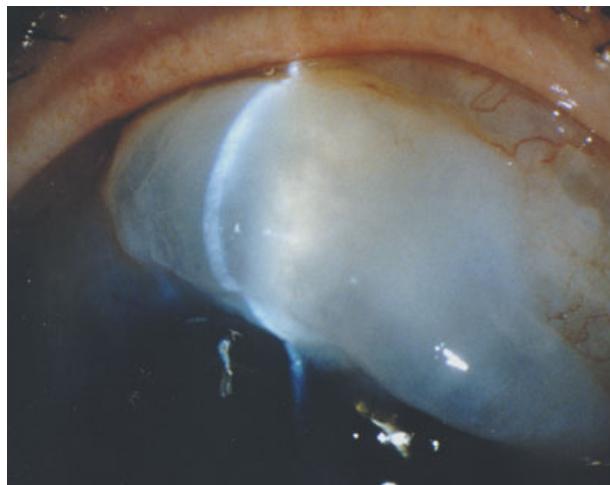
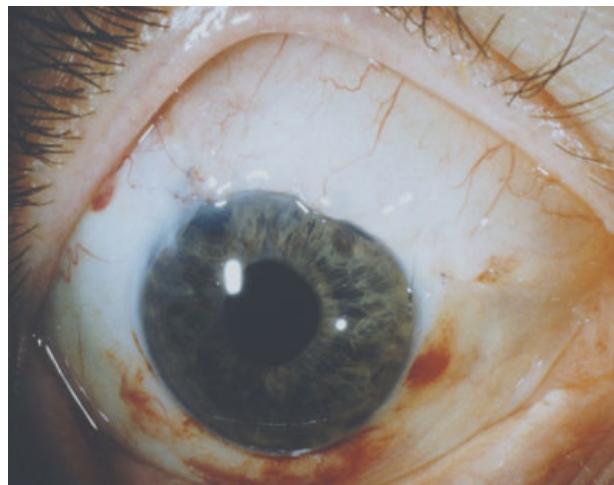


FIGURE 46-3 Appearance of a large, overfiltering bleb after injection of autologous blood into the bleb and a compression patch. Note subconjunctival inflammation and residual blood. The bleb eventually became lower and thicker, with increased intraocular pressure.



A



B

FIGURE 46-4 (A) Overfiltrating and leaking bleb after a trabeculectomy with mitomycin-C. (B) The bleb was later excised and posterior conjunctiva advanced to cover the defect.

Reopen the Conjunctiva and Reinforce the Flap

When more conservative measures fail to raise IOP, the bleb must be surgically revised.⁷⁸ This involves identifying and reopening the original conjunctival incision or creating a more posterior incision. After reinforcing the scleral flap with additional 10-0 nylon sutures, Tenon's capsule and conjunctiva are closed separately with a running 9-0 monofilament Vicryl suture. Including a Tenon's capsule autograft in the wound can further reinforce a thin, attenuated bleb.

A thin scleral flap or a full-thickness opening generally must be reinforced with a slightly oversized patch graft sutured over the flap with 10-0 nylon. This graft can be glycerin-preserved sclera,⁷⁹⁻⁸¹ preserved pericardium, or a corneal allograft.⁸² Unlike a resutured scleral flap, tension on these patch grafts cannot be adjusted with suture lysis and may result in loss of the filtering bleb.

Conjunctival Advancement, Excision, and Transplant

If the bleb is extremely thin or leaking, the surgeon may have to combine reinforcement of the scleral flap with conjunctival advancement^{59,63} or transplantation.⁸³ Advancing a conjunctival flap may involve making a relaxing incision in the conjunctiva and Tenon's capsule near the fornix to allow dissection and mobilization of these tissues from the episclera. The flap is then pulled forward and its anterior edge sutured to the peripheral cornea with 10-0 nylon. The posterior edge is sutured to the sclera or conjunctiva with 9-0 or 8-0 Vicryl (Fig. 46-4A,B).

If conjunctival scarring prevents the creation of a sufficiently mobile flap, then a conjunctival autograft may be necessary (Fig. 46-5). This involves excising the ischemic bleb and measuring the diameter of the defect with calipers. Using a corneal traction suture to rotate the eye upward, an area of inferior bulbar conjunctiva 50% larger than the defect is marked out, excised, and then sutured

to the defect with interrupted 9-0 Vicryl sutures posteriorly and 10-0 nylon at the conjunctiva–cornea interface. The donor site is allowed to heal through granulation tissue.

Both conjunctival advancement and transplantation result in normal conjunctiva over the trabeculectomy site. Additional sutures in the scleral flap are not always necessary and a bleb often re-forms over the original filter.

Lens Extraction

Removal of the crystalline lens can also reverse hypotony, and may be considered if any lens opacity is present, followed by a reassessment of bleb function and pressure control.^{84,85} This approach is supported by the difficulty of differentiating between decreased vision from hypotony maculopathy versus cataract, the fact that 52% of eyes will develop a cataract after trabeculectomy,⁴⁶ and that many of the methods used to treat hypotony can actually accelerate cataract formation.⁴⁰

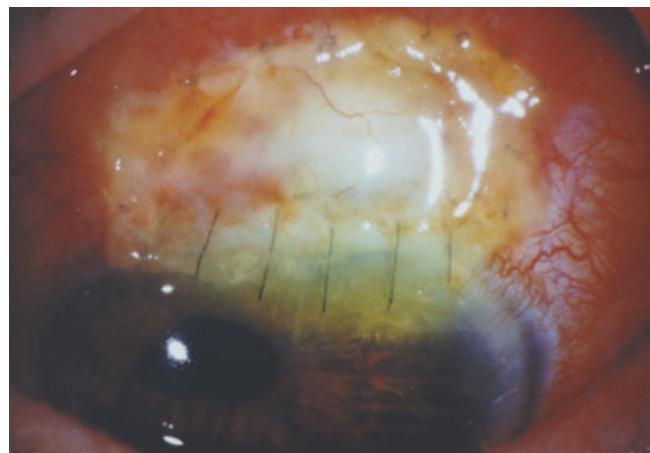


FIGURE 46-5 An eye after excision of a leaking bleb, with the defect covered by a conjunctival autograft from the inferior fornix.

CONTROVERSY

Cataract removal may reverse ocular hypotony following filtration surgery. However, this does not always succeed, and lens extraction in a hypotonous eye presents many challenges.

However, lens extraction in a hypotonous eye presents several challenges. Reduced axial length from hypotony can complicate intraocular lens selection. A diminished view through the soft cornea, and rapid outflow of infused saline through the trabeculectomy site can also complicate phacoemulsification in this situation. Postoperatively, limiting steroid use to enhance inflammation and using aqueous suppressants to decrease the bleb height during the healing and remodeling phase may also help reverse hypotony.

PROGNOSIS

Spontaneous resolution of prolonged hypotony after filtering surgery is uncommon.^{8,13,86} Unfortunately, an increase in the IOP to a normal level does not always resolve the macular changes and return the visual acuity to baseline.^{6,13,66,86,87} Although elevating the pressure to a higher than normal range may successfully flatten the posterior pole,^{47,78,87} photoreceptor loss, choroidal thickening, pigmentary changes, and epiretinal membrane formation can still permanently affect vision.⁸

Some studies demonstrate an association between prolonged hypotony and ultimate failure of the filter and poor visual recovery.^{3,12} For this reason, early intervention (i.e., within 6 months) is often advocated.³ However, reversal of even prolonged hypotony can still occasionally produce a good visual outcome.^{9,73}

Prevention remains the best treatment for hypotony. This includes limiting the use of antifibrotic agents to patients with a low risk for developing hypotony maculopathy, using lower concentrations of these agents for shorter time periods, and conservative suture-lysis. If symptomatic hypotony does occur, the surgeon should consider early intervention and be prepared to use multiple approaches.³

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